Characterizing proprioceptive and haptic function in typically developing children and individuals with chemotherapy-related somatosensory impairment

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Dedication

This dissertation is dedicated to my family.

Abstract

Despite the importance of somatosensation during motor development, a comprehensive characterization of the typical development of somatosensory function in children does not exist. This is largely due to a lack of objective measures with appropriate resolution. Mapping trajectories of typical development of proprioceptive and haptic function is necessary in order to identify sensory deficits in pediatric patient populations with known or suspected proprioceptive and/or haptic deficits. One such population is children treated with chemotherapy for pediatric cancers. Chemotherapeutic agents used to treat cancer generate unwanted side effects including peripheral nerve damage called chemotherapy-induced peripheral neuropathy (CIPN). To date, the magnitude and timeline of somatosensory impairments due to CIPN are not well understood. We have updated a methodology of measuring proprioceptive acuity and developed a novel measure of haptic acuity and sensitivity that are appropriate for use in both adult and pediatric populations. The aims of this study were to apply these two assessment tools to characterize 1) proprioceptive and 2) haptic function during typical development, 3) measure somatosensory-related impairment in individuals treated with chemotherapy for pediatric cancer, and 4) identify relationships between chemotherapy-related somatosensory impairment and therapeutic markers such as cumulative dosage of chemotherapeutic agents. *Methods*: To map the development of proprioceptive acuity, 308 typically developing (TD) children (ages 5-17 years) and 26 adults (ages 18-25 years) performed a forearm position matching task with a bimanual manipulandum. Haptic acuity (discrimination) or sensitivity (detection) was measured using curvature perception assessments in 59 and 56 children respectively (ages 9-12 years). Healthy adults completed both haptic assessments (n = 27, ages 19-25 years). These proprioceptive and haptic assessments were utilized to characterize somatosensory impairment in 15 individuals treated with chemotherapy for pediatric cancers (ages 6-25 years). *Results*: First, proprioceptive development is characterized by a reduction in random limb position matching error, not a change in systematic limb position error. Second, haptic acuity and sensitivity does not change significantly after the age of 9 years. Third, these somatosensory assessments were able to characterize proprioceptive and haptic impairment in individuals treated with chemotherapy for pediatric cancer. 7 of 15 cancer survivors exhibited proprioceptive precision measures above the 75th percentile and 11 of

15 exhibited at least one haptic function measure above the 75th percentile of their age-matched cohort. Fourth, a multiple linear regression model of cumulative dosage of chemotherapeutic agent types predicted 80% of the variability in the haptic discrimination thresholds (adjusted R^2 = 0.80). *Conclusion*: This work generated a complete characterization of the development of proprioceptive acuity in TD children and established haptic function is adult-like by the age of 9 years. This study also demonstrated proof-of-concept for identifying somatosensory deficits in individuals treated with chemotherapy for pediatric cancers. These objective, clinically appropriate, somatosensory assessments and the necessary normative development data established here can identify or monitor somatosensory deficits in pediatric populations with known or suspected deficits.

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List of Abbreviations

AIC – Akaike Information Criterion for variable selection

CIPN – chemotherapy-induced peripheral neuropathy

JND – just noticeable difference

MLR – multiple linear regression

P_{diff} – position difference (between the match and reference arm)

PE – position error (average difference between the match and reference arm)

SDP_{diff} – standard deviation of the position difference (standard deviation of P_{diff})

SEP – somatosensory evoked potential

TD – typically developing (children)

Introduction

Proprioception is the awareness of limb and body position and motion as well as a sense of heaviness (Goldscheider 1898). Proprioceptive signals originate from mechanoreceptors embedded in the joints, tendons, muscles, and skin. Intact proprioception is essential for the control of muscle tone and voluntary movement. Haptic perception refers to “active touch,” that is the moving of hands, fingers or other body surfaces to extract object features such as texture, hardness orientation, or shape (Gibson 1966). Haptic perception relies on proprioceptive signals as well as signals from the skin mechanoreceptors that encode touch-related information such as pressure and texture. Many tasks of daily living that involve object handling and manipulation rely on haptic information (Klatzky, Lederman and Metzger 1985, Kalisch et al. 2012). Similarly, proprioception is essential for the control of muscle tone and voluntary movement. Both of these sensory modalities are essential for the control and development of balance and fine motor function in children and adolescents.

Despite the importance of proprioceptive and haptic information for motor control, the typical development of proprioceptive and haptic function is not well understood. These somatosensory modalities are difficult to measure objectively and with appropriate resolution in children. The lack of universally accepted measures of proprioceptive and haptic function have created a knowledge gap in the understanding of somatosensory development in typically developing (TD) children.

Despite the shortcoming of current sensory measures, numerous pediatric conditions such as cerebral palsy, autism, or developmental coordination disorder are associated with proprioceptive or haptic deficits that adversely affect motor behavior and motor development (Goble, Hurvitz and Brown 2009, Wang et al. 2009, Zwicker, Harris and Klassen 2013, Kaufman and Schilling 2007, Coleman, Piek and Livesey 2001, Li et al. 2015). Consequently, haptic and proprioceptive dysfunction in pediatric populations disrupts somatosensory development, which has long-term consequences potentially contenting into adulthood. Thus, a comprehensive characterization of the development of proprioception and haptics in children is necessary. These normative data are essential for the identification and monitoring of pediatric populations with somatosensory deficits.

One specific application is for chemotherapy-induced peripheral neuropathy (CIPN). CIPN is a common and morbid health consequence of therapy affecting patients treated with chemotherapy for cancer. This is especially of concern with pediatric cancers where sensory injury is occurring during somatosensory development. Current methods of measuring CIPN have the same shortcomings of current somatosensory measures. Given the lack of sensitive, universally accepted measures the time course and extent of recovery from somatosensory impairment in CIPN is poorly understood. Additionally, current measures have been unable to consistently identify the magnitude of sensory impairment associated with specific agents or to understand the efficacy of strategies to prevent CIPN (Moore and Groninger 2013). Moreover, the impact of somatosensory dysfunction due to prolonged chemotherapeutic treatment on sensorimotor development is unknown. At present, few objective data exist on how somatosensation in children is altered during and after chemotherapy treatment (Jain et al. 2014, Lavoie Smith et al. 2013, Moore and Groninger 2013).

We have developed two objective, quick-to-execute, high-resolution measures for proprioceptive and haptic function. The work described here applied these measures to map the development of somatosensation in TD children and to establish the magnitudes of chemotherapy-related somatosensory impairment in patients with pediatric cancer.

Aims

Two separate studies were conducted. The first study characterized developmental norms of proprioceptive and haptic ability to be used as reference for assessing somatosensory deficits in pediatric cancer populations. The second study obtained objective measures of the magnitude of proprioceptive and haptic impairment associated with exposure to chemotherapeutic agents during treatment for pediatric cancer. The studies had the following specific aims:

Aim 1: **Characterize the development of proprioceptive acuity in typically developing children**. A bimanual manipulandum will be employed with a contralateral forearm position matching task to measure both the random and systematic errors in forearm position matching across the developmental span in 10-to-20 children at each year of age between 5 and 17 years and 20 adults ages 18 to 25 years. Presentation and

analysis of developmental trends in forearm position matching errors for children and adults will verify this aim.

Aim 2: Characterize the development of haptic acuity and sensitivity in typically developing children. A haptic block system will be employed with two curvature perception tasks to measure both haptic acuity and haptic sensitivity across the developmental span in 10-to-20 children at each year of age between 5 and 17 years and 20 adults ages 18 to 25 years. Presentation and analysis of developmental trends in haptic acuity and sensitivity for children and adults will verify this aim.

Aim 3: **Establish the magnitudes of proprioceptive and haptic sensory impairment during treatment in individuals treated with chemotherapy for pediatric cancers.** To assess proprioceptive deficits, the bimanual manipulandum and the same forearm position matching task from Aim 1 will be used. Values for the random and systematic position matching errors from the individuals treated with chemotherapy will be compared with the developmental norms generated in Aim 1. Similarly, the haptic acuity and sensitivity assessments from Aim 2 will be applied in this patient population. The haptic acuity and sensitivity thresholds from these individuals will be compared with thresholds from age-matched controls. Individuals in the chemotherapy treatment group with proprioceptive bias or precision measures outside the 75^{th} percentile of the normative data will indicate proprioceptive impairment. Individuals in this group with haptic thresholds greater than the 75^{th} percentile of the age-matched normative cohort will indicate haptic impairment. The presentation of proprioceptive matching task error values and haptic thresholds for this group will verify this aim.

Aim 4: **Identify relationships between observable somatosensory dysfunction and demographic, clinical, and therapeutic markers.** Correlation analyses will be performed to identify variables (age, diagnosis, time since diagnosis, and cumulative dosage of chemotherapeutic agents) that predict observable proprioceptive and haptic impairment. Proprioceptive or haptic assessment outcomes significantly correlated with any of these variables will verify this aim.

Background

Somatosensation includes touch, proprioception, temperature, and pain sensation. This work focuses on the somatosensory components touch and proprioception. In this work, somatosensory measures are specifically referencing these two aspects of somatosensation. Proprioception, or kinesthesia, is also a collective term and includes position sense, passive motion sense, active motion sense, and gravito-inertial sense or a sense of heaviness (Goldscheider 1898). The proprioceptive acuity assessment discussed and applied in this work specifically measures limb position sense acuity. Similarly, haptic perception refers to “active touch,” that is the moving of hands, fingers or other body surfaces to extract object features such as texture, hardness orientation, or shape (Gibson 1966, Gibson 1986). The haptic assessments in this work only measure the ability to perceive shape via active touch, specifically curvature perception.

Mechanoreceptors for proprioception and haptics

Proprioceptive signals originate from mechanoreceptors embedded in the joints, tendons, muscles, and skin. Intact proprioception is essential for the control of muscle tone and voluntary movement. Muscle spindles embedded in muscle tissue are considered the primary sensory organs for limb and body position and motion sense (Gardner and Johnson 2013). The firing rate of muscle spindles is related to the length of the muscle (or stretch) as well as the lengthening velocity (Pearson and Gordon 2013). The structure of the muscle spindle are mature in children by the age of 3 years (Österlund et al. 2011). This suggests that any changes in proprioceptive acuity occurring after the age of three are associated with the somatosensory pathways at the spinal level or higher.

The haptic task in this study involves proprioception as well as tactile or touch sensation using the glabrous skin on the pad of the index finger. The four main mechanoreceptors involved (and the associated fiber type) are the Merkel cells (SA1), Meissner corpuscles (RA1), Ruffini endings (SA2) and Pacinian corpuscles (RA2). Each receptor type has a specific receptor density and receptive fields, but all occur in the pad of the finger. While all of these receptors are likely active during the haptic discrimination and detection tasks applied in this study, the perception of curvature likely relies most on Merkel cells, which encode for edges and form, the Meissner corpuscles, which encode lateral skin movements, and the Ruffini endings, which encode pressure and skin stretch. All four

receptor types are innervated by large (Aα) and medium nerve fibers (Aβ) (Gardner and Johnson 2013).

The afferent sensory information from both the proprioceptive and tactile mechanoreceptors travels through the dorsal column, medial lemniscal, and thalamocortical pathways to the primary somatosensory cortex (Gardner and Johnson 2013). Other cortical areas involved in proprioceptive and haptic perception include the cerebellum and basal ganglia (Lisberger and Thach 2013, DeLong and Wichmann 2009, Wichmann and DeLong 2013, Aman et al. 2014).

Current knowledge of the typical development of limb position sense acuity

Limb position sense acuity improves between 5 and 7 years of age and slowly continues to approach adult levels throughout adolescence (Bairstow and Laszlo 1981, Elliott, Connolly and Doyle 1988, Goble et al. 2005, Laszlo and Bairstow 1980, Visser and Geuze 2000). A comprehensive description of the typical development of limb position sense is not available because of the shortcomings of the applied methods used in previous research, small sample sizes, and/or limited age ranges that were tested. Noted shortcomings aside, previous literature demonstrate a major difference between 5 and 8 years of age so the inclusion of this age group is important for a complete developmental trajectory of proprioceptive acuity (Bairstow and Laszlo 1981, Laszlo and Bairstow 1980, Elliott et al. 1988). Recently, Goble et al. have used contralateral, ipsilateral-remembered, and contralateral-remembered forearm matching tasks to measure limb position acuity in children. These tasks involve a bimanual manipulandum that restrict forearm movement to rotation in the horizontal plane, elbow flexion and extension (Goble et al. 2005). The results of this study are consistent with those discussed above demonstrating changes in limb position sense throughout adolescence (Laszlo and Bairstow 1980, Visser and Geuze 2000). However, compared to earlier studies, which often measured from 100 or more individuals, this study included only 18 participants in two age groups (8 - 10 and 16 - 18 years of age).

Shortcomings of previous measures of limb position acuity in children

There is no established assessment for proprioceptive acuity. This is in part because proprioceptive function is difficult to measure objectively and accurately. Clinical rating scales are useful but often they require significant time, equipment, and specialized personnel (Haryani et al. 2017, Moore and Groninger 2013, Mohrmann, Armer and Hayashi 2017). Meanwhile, they may not have sufficient resolution to detect differences in proprioceptive acuity.

Objectively measuring proprioceptive acuity is further complicated by requirements associated with pediatric populations. Assessments must be simple to understand and incorporate simple movements so motor ability does not affect the proprioceptive measure. The Kinesthetic Sensitivity Test (KST) task used in several studies involved moving both arms simultaneously up two ramp inclines and determining which ramp is steeper (Bairstow and Laszlo 1981, Laszlo and Bairstow 1980). This movement requires rotation at both the shoulder and elbow so this is not a simple movement. Since the arms moves up the ramps against gravity the amount of force, or effort, to move the arms up the different ramp angles while a valid component of proprioception, this is a combination of force applied as well as limb position perception. Elliott et al. noted that for the youngest age group tested, seven children could not differentiate between the largest possible ramp differences of 20°. Twenty five percent of 5 and 6 year old children were correct half of the time or less (which is the same as random guessing) (Bairstow and Laszlo 1981). This demonstrates that the ramp incline differentiation task itself was potentially too difficult to be accurately perceived by children. In addition, the task requires memory of the spatial position of the arms as responses are given after the movement up and back down the ramp. This response delay could further deteriorate the measure, if attention is not maintained. Psychophysical test methods, while the gold-standard method for estimating perceptual thresholds, require a large number of trials. Laszlo and Bairstow noted that the loss of attention in children is of concern for measures with more than 30 trials without breaks (Bairstow and Laszlo 1986).

Livesey et al. developed a Kinesthetic Acuity Test (KAT) method with passive center-out movements in the horizontal plane (Livesey and Intili 1996). While the movement of this test is perpendicular to gravitation forces, the outcome measure is the correct number of

responses out of the total number of trials (Livesey and Intili 1996, Livesey 2002). Although this percent correct score type is informative, it does not provide information about the components of acuity, meaning it does not differentiate random and systematic errors. The same scoring system was also used with the KST ramp method. This type of score is not a weighted score and does not indicate the difficulty level of the stimulus for each correct or incorrect response. Compared to a raw error measure (magnitude), this type of measure confounds systematic errors in kinesthetic acuity with response variability. For example, individual responses may have larger magnitudes of absolute errors compared with an adult, while the mean raw error can still be similar. The difference is a greater variability in the child's responses compared to an adult. A correct/incorrect response recording method that is not weighted cannot obtain this information.

Thus, the methods and outcome measures utilized in the study of kinesthetic acuity have provided a vague trajectory of the development of limb position sense. Moreover, these assessments have not been able to consistently differentiate KAT assessment to differentiate children with Developmental Coordination Disorder (DCD) from typically developing children (Hoare and Larkin 1991, Lord and Hulme 1987, Piek and Coleman-Carman 1995). However, the coarse scale of the test and a non-weighted total of correct responses, likely contributed to the fact that significant differences between these groups were not always found (Hoare and Larkin 1991, Lord and Hulme 1987).

Equipment and procedural design for object assessment of limb position acuity

Ideal assessments are objective, require minimal equipment, and are easily administered as specialized staff are generally not available in clinical settings (Haryani et al. 2017, Mohrmann et al. 2017). In addition, to be accepted for clinical use an assessment must be completed quickly to reduce the demands on staff as well as address the fact that assessments require high levels of attention and younger children can only focus on the sensory assessment for a short period of time. Finally, equipment must appropriately scale to the anthropometrics of all participants ranging from small children to large adults. The proprioceptive assessment must be appropriate for the modality of proprioception one desires to measure, position or motion sense. Position sense is easier to assess with a non-motorized system as precise control of movement velocity is not required. Next, one

needs to select if acuity or sensitivity will be measured. Sensitivity is defined as the ability to detect a stimulus where acuity is the ability to discriminate or compare between two similar, detectable stimuli.

Based on the work of Goble et al. and Elangovan et al., we designed a bimanual manipulandum to address these requirements (Goble et al. 2005, Goble 2010, Elangovan, Aman and Konczak 2014a, Elangovan, Herrmann and Konczak 2014b). The manipulandum was used here to quickly, objectively, and precisely measure position sense acuity via a contralateral arm position matching task. The contralateral task removes the cognitive requirement of remembering a previously presented position that is a component of ipsilateral matching tasks (Elangovan et al. 2014b, Goble et al. 2005, Goble 2010). The method utilized by Goble et al., involves active motion to match the position of a passively moved reference limb. Employing active matching movements is a trade-off that allows for numerical error measures in limb position matching without the large number of trials required for psychophysical methods. The potential confound between motor ability and limb position sense acuity can be reduced by allowing the participants as much time as desired to match the limb position. Goble et al. also address that the type of joint matching task utilizes various neural structures in addition to the primary somatosensory area (Goble 2010). For example, a contralateral matching task requires transfer of sensory information between hemispheres and ipsilateral tasks utilize memory to match position so impairments or the development of the structures required for these processes may confound the limb position sense acuity measure (Goble et al. 2005, Goble 2010).

The limb position matching tasks described by Goble et al. are an improved measure of limb position sense acuity as one can separate the components of acuity, bias and precision, while keeping the length of testing to a minimum. Bias is an indication of systematic error, or how close a response is to the target (I.S.O 1994). Precision is defined as the random error, or the spread in repeated responses (I.S.O 1994). Both of these characteristics of acuity can be measured with the limb position matching equipment and assessment utilized here (see Figure 1 for a visual depiction of bias and precision).

Using a joint position-matching task for assessing proprioceptive acuity is a hybrid assessment that involves both a passive sensory stimulus and an active response to

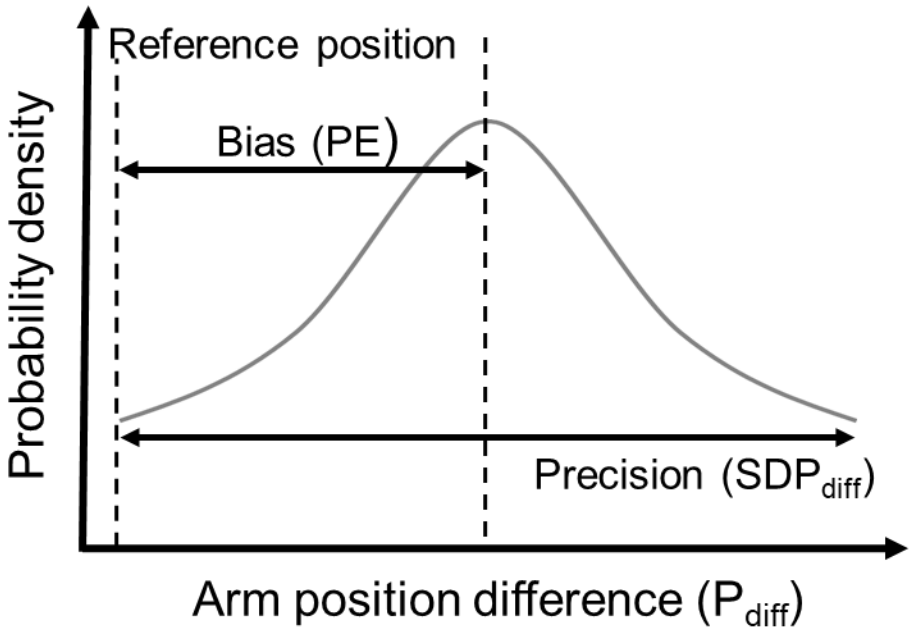

Figure 1: Hypothetical probability distribution of the limb position matching errors with the components of acuity labeled. Bias represents systematic error in limb position matching and precision represents random error in limb position matching responses. Modified from Holst-Wolf et al. 2016 Figure 1a.

match the reference limb position. This hybridization allows for quick and objective calculation of limb position acuity as well as a more natural assessment of proprioceptive acuity than pure passive measures. However, the active matching generates an efference copy of the motor command of the movement that is available to the central nervous system to predict the movement outcome (Wolpert, Pearson and Ghez 2013). This means that the active joint-position-matching task is not a pure sensory measure and responses may be influenced by: 1) the internal predicted sensory information for the matching movement, 2) the processing of afferent sensory information of the moving limb, and 3) the integration of these two pieces of information to generate a percept of the forearm positions (Konczak et al. 2012, Blakemore, Frith and Wolpert 2001, Von Holst 1954). Similarly, developmental differences in motor ability could affect the responses in the limb position matching assessment. To minimize this potential confound, the movement task was simplified (single joint, one degree-of-freedom, flexion/extension movement of the elbow, forearm movement in the horizontal plane perpendicular to gravity). Participants were given as much time as desired to achieve the desired forearm position. The limb position measure was made at rest so it emphasized the limb position, not the movement to achieve that position. These factors minimize any potential influence of movement

ability (movement acceleration or speed) on the desired perceptual measure. The limb position-matching task via bimanual manipulandum is not perfect, but generates informative measures of acuity in a relatively short time span which is ideal for measuring the development of proprioception in children. For these reasons, it was used here as an objective measure of proprioceptive acuity.

We assessed proprioceptive acuity at three different positions as Goble et al. have demonstrated that higher amplitudes of limb displacement is associated with higher limb position matching error (Goble et al. 2005). To account for possible differences in limb position acuity across the workspace, we included a near, intermediate, and extended position (40º, 60 º, and 90 º target positions) within the typical forearm/elbow joint range of motion.

Typical development of haptic function

Haptics requires active touch and the involvement of multiple sensory modalities so the development of haptic acuity and sensitivity depends on several components including the development of individual sensory modalities, motor behavior to execute exploratory procedures, and integration of sensory information from multiple modalities. Evidence in animal models and pre-term human infants suggest that tactile stimulation is functional before birth and it plays an important role in perceptual and cognitive development (Lickliter 2000, Weiss 2005, Parsons et al. 2010). Haptic perception, which requires active touch, is also functional in infancy. Rose et al. have demonstrated that at 12 months infants discriminate between different shapes by noting that infants spent more time handling novel shapes than ones that were previously handled in a familiarization condition (Rose, Gottfried and Bridger 1981). Similarly, Rochat demonstrated that three month old infants can discriminate between hard and soft objects manipulated in the hand further demonstrating the functionality of early haptic perception (Rochat 1987). An important component of this finding was how discrimination was measured, by how the object was handled by the infants. They either held the assessment object in a clutch grasp or in quick squeeze-release pattern. This demonstrates that the motor ability necessary to assess certain object properties such as hardness or softness is also functional in infancy. As haptics requires active touch, a comment on motor development is appropriate for discussing haptic related object manipulation. Kalagher et al. found that

haptic exploratory procedures in children ages 3 to 5 years were adult-like, meaning typical motor development for grasping and individual finger movements are functional by this age and allow for the same hand movement patterns adults use to assess object properties through active touch (Kalagher and Jones 2011, Lederman and Klatzky 1987).

Studies investigating the development of tactile sensitivity, rather than simple functionality, such as moving two-point discrimination have shown that this type of tactile perception appears to be adult-like by the age of 4 years old (Hermann Richard, Novak Christine and Mackinnon Susan 1996). However, haptic size discrimination is still maturing in 8-10 year old children (Gori et al. 2008). In a study of curvature discrimination using a robotic manipulandum, Gori et al. also demonstrated that haptic acuity is improving throughout childhood and is not adult-like by the age of 14 years (Gori et al. 2012). While these are important general findings none of these studies have mapped haptic acuity across the entire developmental span. Gori et al. have come the closest measuring haptic acuity from ages 6 to 14 years but their study only included 33 children in this age range which is not sufficient to estimate normative percentiles for haptic maturation across development.

Equipment and procedure for objective assessment of haptic function

Haptic assessments are multimodal assessments meaning they require active touch or exploratory procedure and perception of at least two sensory modalities, typically touch and proprioception. A commonly employed haptic paradigm is object recognition via haptic exploration with the hand. This type of assessment provides information about the functionality of haptic perception but does not easily provide for measure of acuity and sensitivity. Here *acuity* is defined as the ability to discriminate between two stimuli and *sensitivity* is the ability to detect a stimulus. The system used by Gori et al. (2012), which created virtual curvatures via a robotic manipulandum, could measure both aspects of haptic perception. However, this equipment is expensive, requires specialized personnel, and is not portable. Additionally, the psychophysical method employed required 40 trials, a significant amount of time. Thus, it was not well suited for use with children or in a clinic setting. We designed a modified version of this assessment by manufacturing a set of plastic blocks with set curvatures. This set of haptic curvature blocks could be used with the same 2-option-forced-choice paradigm to measure either haptic acuity or sensitivity. We also identified a different psychophysical threshold

adaptive algorithm typically employed in visual perception research that required fewer trials to estimate a perceptual threshold (Prins 2013). Thus, we created a portable haptic curvature assessment that does not required specialized personnel and can be completed in 20 or 25 trials. Individuals were allowed to self-select the number of lateral finger movements ($\geq$4 times), the movement kinematics (velocity, acceleration), and the magnitude of the block surface explorations (did the movements remain in the middle of the block or move all the way to the lateral surface edges). The intent of minimizing limitations was to simplify the haptic assessment so individuals could focus on the perceptual task without having to continually attend to the rules. This allowed for a more ecological test measure as well as one that was appropriate for younger children. We did not measure kinematics of haptic exploration and purposely placed minimal limitations on haptic exploration. Individuals were not provided a strategy for haptic exploration. However, the application of systematic strategy in the two haptic tasks (discrimination and detection) may result in different weighting of sensory afferents. For curvature detection, a strategy of horizontal hand movement may be employed with emphasis on the perception of the pressure on the finger pad. For discrimination, a strategy of attempting to maintain constant pressure on the pad of the finger while focusing on the perception of the hand/forearm movement trajectory may be employed. Essentially, the strategy being maintaining constant input from one type of sensory information while focusing on the perception of changes in the other sensory modality. There is nothing wrong with adapting different strategies for the assessments but this was not controlled for and needs to be acknowledged when interpreting the results of the two haptic assessments.

Chemotherapy induced peripheral neuropathy (CIPN)

In the U.S. approximately 15,000 children and young adults are diagnosed with cancer every year (Childhood Cancer Research Fund, 2017). While the 5-year-survival rate has reached 80%, there are many potential short- and long-term health consequences related to prescribed therapies (Childhood Cancer Research Fund, 2017). CIPN is a common and morbid health consequence affecting patients with pediatric cancers. Exposure to multiple classes of chemotherapeutic agents can cause peripheral nerve damage (Tracy, Tracy and Dyck 2008, Seretny et al. 2014). However, there is no gold standard for measuring peripheral neuropathy, making it difficult to identify the incidence rates of CIPN in children.

Estimates for neuropathy incidence range from 3% up to 78% in pediatric populations, noting each study used different measures and definitions of CIPN (Moore and Groninger 2013, Lavoie Smith et al. 2015). It is understood that the negative effects of chemotherapy correlate with the type of agent, number and cumulative dosage of agents as well as the time since administration of the agents (Moore and Groninger 2013). Higher incidents rates are typically found in populations treated with a combination of agents that include vinca alkaloids like vincristine (Moore and Groninger 2013, Lavoie Smith et al. 2015). However, the lack of clinically appropriate, high-resolution measures of CIPN make it difficult to perform consistent and objective assessments over time to characterize the timeline of the effects (Moore and Groninger 2013, Mohrmann et al. 2017, Haryani et al. 2017).

Current assessments of CIPN in children

Nerve conduction velocity has been found to be abnormal during chemotherapy in up to 87% of individuals treated for pediatric cancers (Kava et al. 2017). However, nerve conduction velocity measures in the clinic typically requires involvement of a neurologist. This measure also requires specialized equipment as well as being an uncomfortable procedure so this measure is not standard practice during chemotherapy treatment. The Pediatric-Modified Total Neuropathy Score (ped-mTNS) (Gilchrist and Tanner 2013) has been used to get an overall measure of CIPN. While the validity and repeatability of this rating scale has been documented, the measures rely in part on subjective patient responses (Gilchrist and Tanner 2013, Gilchrist, Marais and Tanner 2014). Moreover, the non-interview components of the ped-mTNS, such as monofilament testing, vibration testing, light touch sensation, manual muscle testing, and deep tendon reflex measures require an array of tools and personnel with significant training to reliably and repeatedly administer these test components (Gilchrist and Tanner 2013). Lavoie Smith et al. have created another rating scale very similar to that of the ped-mTNS called the Total Neuropathy Score – Pediatric Vincristine (TNS©-PV) (Lavoie Smith et al. 2013, M. et al. 2015). This assessment is similar to the ped-m TNS with the inclusion of subjective patient assessment of symptoms, temperature sensitivity, vibration sensitivity, muscle strength, tendon reflexes, autonomic symptoms, and laryngeal symptoms (Lavoie Smith et al. 2013). While useful, these rating systems require a significant amount of time to complete making repeated measures over time a concern as they can become burdensome for both

hospital staff and the patients (Haryani et al. 2017). While the components of the ped-mTNS and TNS©-PV target a broad range of sensory fibers, they neglect large-fiber based proprioception, which is a key component of functional motor behavior, leaving the magnitude of proprioceptive impairment due to CIPN unknown. To our knowledge, there are no objective measures of proprioceptive and haptic function currently in general clinical use in pediatric oncology.

While the effects of chemotherapy may be temporary, there are indications that somatosensory impairment persists past treatment. A cross-sectional assessment of nerve conduction velocity and reduced Total Neuropathy Score in pediatric survivors (within 3 years of treatment) of acute lymphoblastic leukemia found 33% were identified with neuropathy by either measure (Jain et al. 2014, Haryani et al. 2017). Another study demonstrated that a proportion of adult survivors of pediatric extracranial cancers treated with vinca alkaloids or platinum-based chemotherapies have been shown to have neuromuscular (17.5%) and sensory (20%) dysfunction when measuring with dorsiflexion strength and the modified Total Neuropathy Score, respectively (Ness et al. 2012, Ness et al. 2013). Furthermore, somatosensory dysfunction is associated with poor mobility and endurance in these adults (Ness et al. 2013). Surveys aimed at establishing functional physical performance deficits in long-term survivors of pediatric cancers have found that survivors are more likely than their non-treated siblings to report limitations that affect self-care, performance of routine activities, and the ability to attend work or school (Ness et al. 2005).

In the final component of this study, we applied the proprioceptive and haptic assessments in a group of individuals treated with chemotherapy for pediatric cancer. These assessments provided an objective evaluation of chemotherapy-related proprioceptive and haptic effects. The haptic acuity and sensitivity assessments were included to evaluate distal peripheral nervous system pathways and mechanoreceptors. Evidence suggests CIPN symptoms often present with the stocking-and-glove neuropathy pattern (Moore and Groninger 2013). The haptic assessments were recently shown to have appropriate resolution to differentiate between typically developing children and children with DCD that have mild to moderate somatosensory impairment (Tseng et al. manuscript in preparation 2018).

Methods

Study 1 participants: TD children and healthy adults

Adult participants were recruited at the University of Minnesota and at the Minnesota State Fair. All younger participants were recruited from a local primary school or at the Minnesota State Fair. Appropriate consent, and when appropriate assent, was obtained before data collection. The study was approved by the University of Minnesota Internal Review Board. All participants reported no central or peripheral nervous system disease or disorder, no implanted medical devices in the arms, and no upper limb injury that would impair the ability to sense limb position or the sense of touch. Inclusion criteria also required that participants were able to attend to the assigned assessments for 5-20 minutes (with breaks as needed). All subjects completed a modified Edinburgh handedness inventory to determine the dominant limb for testing.

Table 1: TD and healthy adult participants that completed the proprioceptive acuity assessment.

Group	Age Range (years)	N	Male/Female
Children	5-17	308	127/181
Adults	18-25	26	12/14

Table 2: TD and healthy participants that completed at least one of the haptic acuity assessments.

Assessment	Group	Age Range (years)	N	Male/Female
Discrimination	Children	9-12	59	29/30
Detection	Children	9-12	56	24/32
Discrimination and Detection	Adults	19-25	27	12/15

Study 2 participants: individuals treated with chemotherapy for pediatric cancers

All patient participants were recruited at the Journey Clinic which is the University of Minnesota Masonic Children's Hospital Pediatric Oncology Clinic. Appropriate consent,

and when appropriate assent, was obtained before data collection. The study was approved by the University of Minnesota Internal Review Board and Cancer Protocol Review Committee. All patient participants reported no central or peripheral nervous system disease or disorder, no implanted medical devices in the arms, and no upper limb injury that would impair the ability to sense limb position and the sense of touch. Patients were also excluded if they had a cranial cancer diagnosis. Inclusion criteria required that participants were able to attend to the assigned assessments for 5-20 minutes (with breaks as needed). The final inclusion criteria was that the individual had been given some form of chemotherapy for a pediatric cancer such as vinca alkaloids (like vincristine or vinblastine). All subjects completed a modified Edinburgh handedness inventory to determine the dominant limb for testing. One child completed two of the assessments but was removed from the study due to lack of compliance with task instructions, their data is not included here.

For table of chemotherapeutic agent types and chemotherapeutic agents given to each individual see Appendix I.

Table 3: Characteristics of patient participants that completed at least one of the proprioceptive and/or haptic acuity assessments.

Group	Age (years)	M/F	Diagnosis	Time since diagnosis (months)
Children	6	M	Lymphoma	17
	9	M	Langerhan's cell histiocytosis	17
	10	F	Ewing's sarcoma	18
	13	F	Leukemia	22
	16	F	Ewing's sarcoma	23
	17	F	Nodular sclerosis, Hodgkin's lymphoma	1
Adults	18	M	Ewing's sarcoma	34
	18	M	Leukemia	38
	19	F	Hodgkin's lymphoma	4
	20	F	Acute lymphoblastic leukemia	14
	21	F	Hodgkin's lymphoma	39
	21	M	Leukemia	20
	24	F	Malignant neoplasm	132
	24	F	Lymphoma, pancreatic tumor	39
	25	F	Leukemia	47

Apparatus: proprioceptive acuity assessment

A bimanual manipulandum with one degree of freedom in the horizontal plane was used to perform bilateral arm position matching as the proprioceptive acuity assessment. Two U.S. Digital H6 optical encoders (2500 quadrature count/revolution spatial resolution: 0.14º), housed at the rotating point of the manipulandum lever arms, recorded the angular position of each arm.

Procedure: proprioceptive acuity assessment

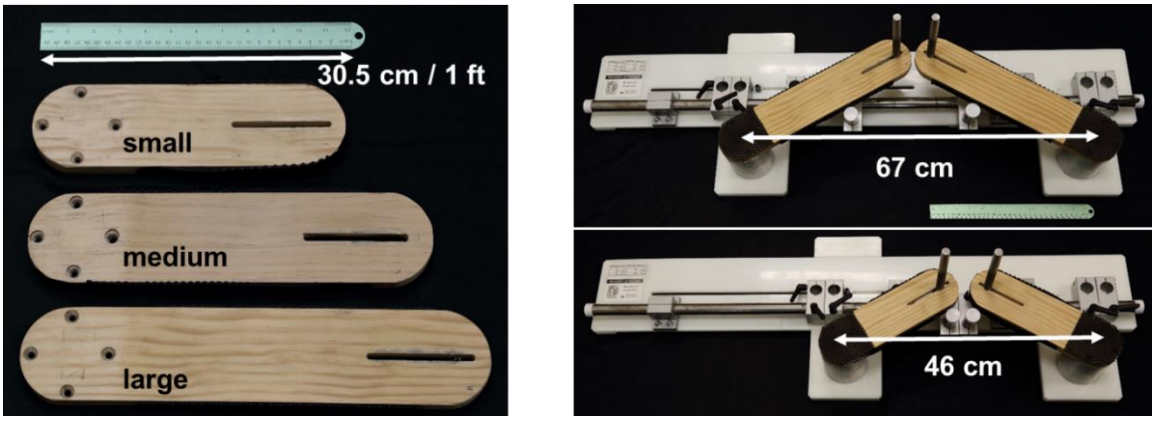

Figure 2: Manipulandum lever length, handle placement, and elbow/shoulder width flexibility of the bi-manual manipulandum are adjustable to conform to the user's anthropometrics. Modified from Holst-Wolf et al. 2016 Figure 1c and 1d.

Participants placed each forearm onto one of the manipulandum levers. The lever arm length and handle placement was adjustable such that the center of rotation of the elbows was directly over the encoders while the participant comfortably gripped the handles. The distance between the two levers could be adjusted such that the participants' elbows were a comfortable distance apart. An adjustable height chair was used to get the appropriate angle between the upper arms and forearm so that the forearms were approximately just above waist height (45° to 85° of shoulder abduction) with the participant seated. Between target positions participants rested each arm in front of the torso at a reference (or start) position set at 30° from the frontal plane (see Figure 3). During testing the non-dominant arm was passively moved in the horizontal plane away from the body at a consistent speed of 20°–30°/second to one of three target positions, 40°, 60°, or 90° from the frontal plane of the participant. Once the researcher moved the non-dominant arm to a target position, the participant was asked to move the dominant arm to match the position of the other arm. Target positions were presented in pseudo random order such that each position

was repeated 5 times for a total of 15 trials. Three different target positions were included as increasing the amplitude of the limb displacement is associated with greater error (Goble et al. 2005) and we here sought to account for possible developmental differences of position sensing across the forearm workspace. Participants had as much time as desired to match the position and when given the verbal ready signal by the participant, the researchers recorded the position of each arm at 60Hz for 1.6 seconds (70 samples). Once the recording finished for that trial the researcher moved the non-dominant hand back to the reference position and gave a verbal cue for the participant to actively move the dominant arm back to the reference position. Participants wore vision occluding glasses during all trials so their arms were not in view. Participants were instructed to match the position of the arms by perceiving their position. One or two practice trials preceded data collection to ensure the instructions of the task were understood before data collection began. If the researcher or child visibly moved during the 1.6 second recording, for example if an arm was brought back to the start position early, the trial was repeated or the trial data was truncated at the point the movement towards the reference position began and a new average was calculated with the truncated data (mean of fewer than 70 samples).This assessment requires approximately 5-10 minutes to complete depending on how long the individual takes to find the desired forearm matching position and if the participant requests any breaks during the 15 trials. (This procedure was previously described in Holst-Wolf et al. 2016.)

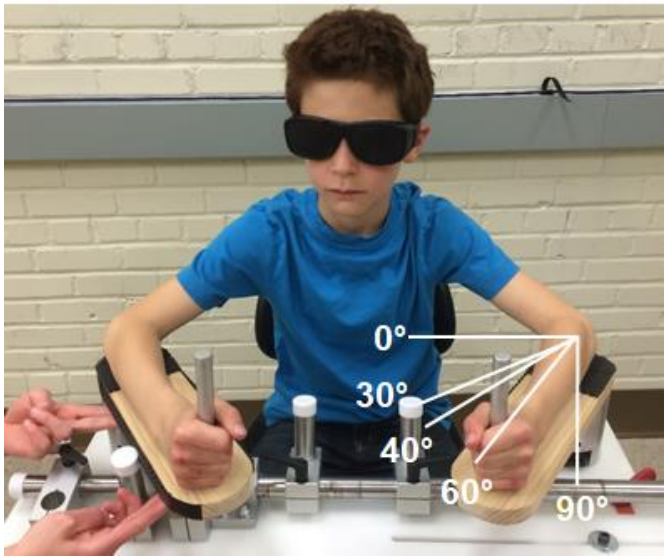

Figure 3: A child seated at the bi-manual manipulandum performing bi-lateral, concurrent forearm position matching. The starting position (30˚) and the three target positions (40˚, 60˚, and 90˚ elbow extension) are shown for reference. Modified from Holst-Wolf et al. 2016 Figure 1b.

Measures: proprioceptive acuity assessment

The physical position of each forearm is defined as the average of the 70 samples recorded over 1.6 seconds. The average position of the dominant matching arm was subtracted from the average position of the reference arm for each trial (P_{diff}).

$$Pdiff = position_{match\ arm} - position_{reference\ arm}$$

For each participant, the position error (PE) was then calculated as the mean of P_{diff} across the five trials for each of the target positions (40°, 60° and 90°).

$$PE_i = \left(\sum_{1}^{n} P_{diff,i}\right)/n \qquad \textit{where n is the number of trials in each condition } (\mathrm{n} = 5) \textit{ and i is } 40°, 60°, 90°$$

Similarly, the corresponding standard deviation (SDP_{diff}) for each participant was calculated as the standard deviation of the five P_{diff} across the five trials for each target position. PE is an indicator of bias, or systematic error, while SDP_{diff} denotes the precision of forearm position matching for each individual.

$$Standard\ Deviation\ (SDP_{diff}) = P_{diff,i} \qquad where\ i\ is\ 40°, 60°, 90°$$

To create an overall limb position acuity score, the percentiles of PE and SDP_{diff} for each age group and target position were calculated (early childhood: 5-6, middle childhood: 7-9, late childhood: 10-11, adolescence: 12-17, and adults 18-26 years old) (Payne 2008).

To generate a single proprioceptive bias and precision score for each individual's bias and precision measures, the average of each individual's 3 bias percentiles and 3 precision percentiles were calculated.

$$Proprioceptive\ Bias\ Score = \overline{(\%PE_{40}, \%PE_{60}, \%PE_{90})}$$

$$Proprioceptive\ Precison\ Score = \overline{(\%SDP_{diff40}, \%SDP_{60}, \%SDP_{90})}$$

The average of all 6 percentiles (bias and acuity) were calculated for each individual to give them an overall limb position acuity score (units are percentile).

$$Proprioceptive\ Acuity\ Score = \overline{(\%PE_{40}, \%PE_{60}, \%PE_{90}, \%SDP_{diff40}, \%SDP_{60}, \%SDP_{90})}$$

For all study participants, each participant's age at the date of data collection was calculated in years and months and converted to a decimal in base 10 (a year was divided into 10 equal sections).

Apparatus: haptic acuity and sensitivity assessments

This system includes a set of high precision custom-made plastic blocks (tolerance < +/- 0.1 mm). Blocks have identical width and length (20 mm x 150 mm). Each block has a defined curvature, heights vary from flat (30mm center-point-height) to highly curved (50 mm center-point-height).

Figure 4: Left – an individual explores the curved surface of a block in a lateral, side-to-side, motion of the index finder of the dominant hand. The haptic curvature block system with center point curvatures from – 0mm (flat) to 20mm center point height. The base of each block is 150 mm long x 30mm high x 20mm wide. The curvature height is added to the base height so the block with the most curvature has a center-point-height of 30mm + 20mm = 50mm. Modified from Tseng et al. manuscript 2018 Figure 1a and 1b.

Procedures: haptic acuity and sensitivity assessments

For the haptic acuity assessment (discrimination), the participant manually explores two curved blocks per trial, one after another. The index finger of the dominant hand probes the surface curvature of the presented block up to four times with lateral (back-and-forth) finger/forearm movements. After exploring the two blocks, the participant verbally indicated which block is more curved. The binary response 'first' or 'second' is coded by correctness, which depends on the random presentation order of the blocks (1 for correct and 0 for incorrect). The correctness is entered by the experimenter into custom-built software and an adaptive algorithm selects the next stimuli difference based on response correctness and past differences in curvature. After 20 trials, the program fits a logistic Weibull function to the response data (Prins 2013) and calculates the haptic just-noticeable-difference (JND) discrimination threshold, an objective measure of haptic function. The haptic sensitivity assessment (detection) utilizes the same probing method as the acuity assessment but only one block is presented in each trial. The participant is then asked to verbally indicate if the block is 'flat' or 'curved.' The binary response is coded by correctness (1 or 0) and entered into the custom software. The adaptive algorithm selects the next stimuli based on the correctness of the response and the stimuli magnitude. The flat block is presented 5 times throughout the assessment in pseudo-random order (once in every 5 trials). After 25 trials, the program fits a logistic Weibull

function to the response data (Prins 2013) and calculates the haptic just-noticeable-difference (JND) detection threshold. Participants wear opaque glasses to occlude vision of their hand and forearm for both the haptic acuity and sensitivity assessments.

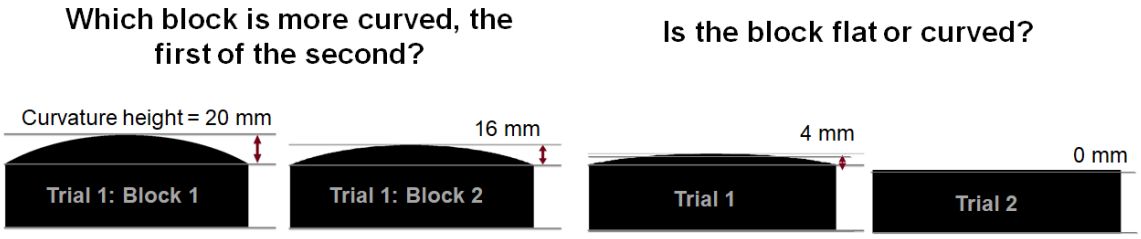

Figure 5: Block presentation of one trial for each the haptic acuity (discrimination) task on the left, and the haptic sensitivity (detection) task on the right. Modified from Tseng et al. 2018 Figure 1c.

Measures: haptic acuity and sensitivity assessments

The adaptive algorithm used by both the haptic acuity and sensitivity assessments selects stimuli based on the correctness of the previous response and the previous stimulus magnitude. After 20 trials for the acuity assessment and 25 trials for the sensitivity assessment, the program fits a logistic Weibull function to the response data (Prins 2013) and calculates the haptic just-noticeable-difference (JND) discrimination or detection threshold respectively.

Study design

Study 1: The characterization of proprioceptive acuity across development study had a cross-sectional design including children ages 5 to 17 years old and adult references ages 18 to 26 years old. The characterization of haptic acuity and sensitivity (discrimination and detection) was a cross-sectional study. Adults completed both the haptic acuity and sensitivity assessments and most children completed both assessments with a subset completing only one of the two. The presentation order of the haptic assessments was pseudo-randomized to minimize any potential effect of fatigue.

Study 2: The investigation of somatosensory impairment in individuals treated with chemotherapy was also a cross-sectional study. Each individual completed the proprioceptive acuity assessment and most completed both of the haptic assessments. One individual opted out of the haptic acuity assessment and one individual opted out of

the haptic sensitivity assessment. The presentation of the three somatosensory assessments was pseudo-randomized to minimize any potential effect of fatigue.

Measures: demographic, clinical, and therapeutic markers

The cumulative dosage of each chemotherapeutic agent prescribed was tabulated for each individual treated with chemotherapy for pediatric cancers. Units are typically in mg/m^2 or mg though some individual agents are in mg/kg or IU/m^2. All dosages of individual agents were in the same units except for vincristine which is in mg/m^2 or mg. The latter is used in instances where the limit on the total amount of vinca alkaloids allowed to be given to a single individual based on body weight was reached. As there were 28 different chemotherapeutic agents prescribed the cumulative dosage of agents were grouped by agent type (see Table 4). Types are differentiated by the chemical composition of the agents and the mechanism of how the agents react on a cellular level (Chemocare.com 2018). For example, alkylating agents are a group of several different chemicals that are cell-cycle non-specific while plant alkaloids are a group of several chemical compounds derived from plants that are cell-cycle specific, meaning their cellular level affects are specific to a certain cell division phase (Chemocare.com 2018). Time since diagnoses was calculated as the time since the date of test to the time of initial cancer diagnoses rounded to the nearest month for each individual.

For all study participants, each participant's age at the date of data collection was calculated in years.

Table 4. The chemotherapeutic agents (units) prescribed to the individuals in this study grouped by agent type. For clarity, when 1) only a single agent is used within an agent type and 2) for the antineoplastics (miscellaneous agents), the agent name listed on the right will be used in this document.

Agent Type	Therapeutic Agents (units)
Plant alkaloids	Vincristine (mg/m^2 or mg), Vinblastine (mg/m^2), Vinorelbine (mg/m^2)
Anti-tumor antibiotics	Bleomycin (IU/m^2), Anthracycline (mg/m^2)
Alkylating agents	Ifosfamide, Procarbazine, Cyclophosphamide, Carmustine (all mg/m^2)
Antimetabolite	Nelarabine (mg/m^2), Methotrexate (mg), Mercaptopurine (mg/m^2), Thioguanine (mg/m^2), Cytarabine (mg/m^2), IT ara-c (mg)
Antineoplastic	PEG-asparaginase (IU/m^2), Brentuximab (mg/kg), Topotecan (mg/m^2)
Topoisomerase inhibitors	Etoposide (mg/m^2)
Enzyme	Erwinia (IU/m^2)
Signal transduction inhibitor	Imatinib (mg)
Monoclonal antibody	Rituximab (mg/m^2)
Cranial radiotherapy	Cranial XRT (cGy)
Glucocorticosteroid	Prednisone (mg/m^2), Dexamethasone (mg/m^2), Hydrocortisone (mg)

Results

Development of limb position sense: bias and precision in TD children and healthy adults

The individual responses of P_{diff}, measuring limb position sense, from all 334 typically developing and adult controls were distributed about zero degrees (zero error) across all ages for each of the three target positions (see Figure 6). The next step was to characterize the components of acuity bias and precision. To characterize systematic changes in bias across development, a repeated measures ANOVA on PE was performed (chronological age x 3 target positions x 2 gender x 2 handedness). There were no significant main effects on PE ($p > 0.05$) indicating that chronological age, target position, handedness, and gender did not affect PE. There was a significant interaction between target position and age ($p = 0.048$), but linear regression of PE by chronological age were not significant for the 40º and 60º target positions. The regression of PE by chronological age for the 90° target position was significant ($p = 0.04$). Yet, the adjusted coefficient of

determination for this linear model indicated that chronological age only explained 1% of the variability in PE_{90} ($R^2_{adjusted}$ = 0.01).

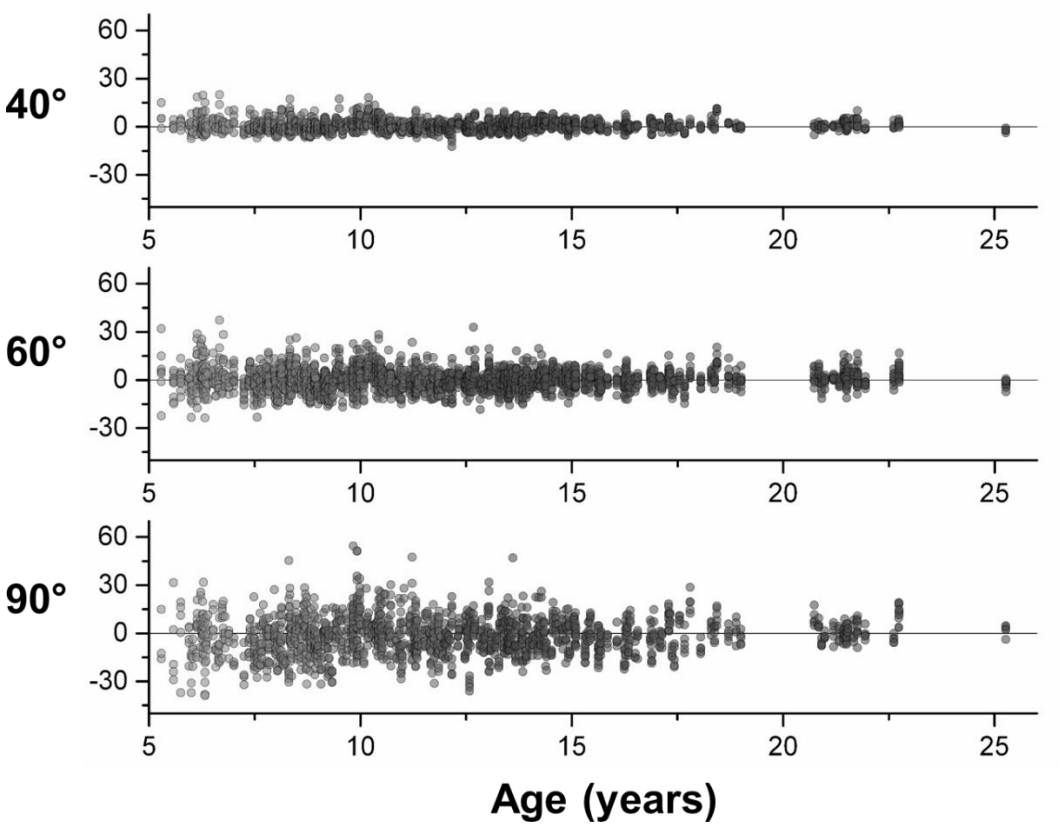

Figure 6: Forearm limb position matching (Pdiff) data for all typically developing children (n = 308) and adults (n = 26) that completed the proprioceptive acuity assessment for each of the three target positions. Modified from Holst-Wolf et al. 2016 Figure 2.

To address development-related change in precision the SDP_{diff} data were analyzed. The SDP_{diff} data distribution was non-normal so this was corrected with a log (base 10) transformation. A repeated measures ANOVA of the log transformed data (chronological age x gender x target position x handedness) found no significant main effects or interactions of gender and handedness ($p < 0.05$). A reduced model (chronological age x target position) revealed significant main effects of both chronological age and target amplitude ($p < 0.001$ for each) but no significant interaction. These indicate that precision is influenced by both age and target amplitude. Non-linear quantile regression procedures were utilized to estimate the percentiles for SDP_{diff} across age for each of the three target positions. For each amplitude, SDP_{diff} decreased as age increased (see Figure 8).

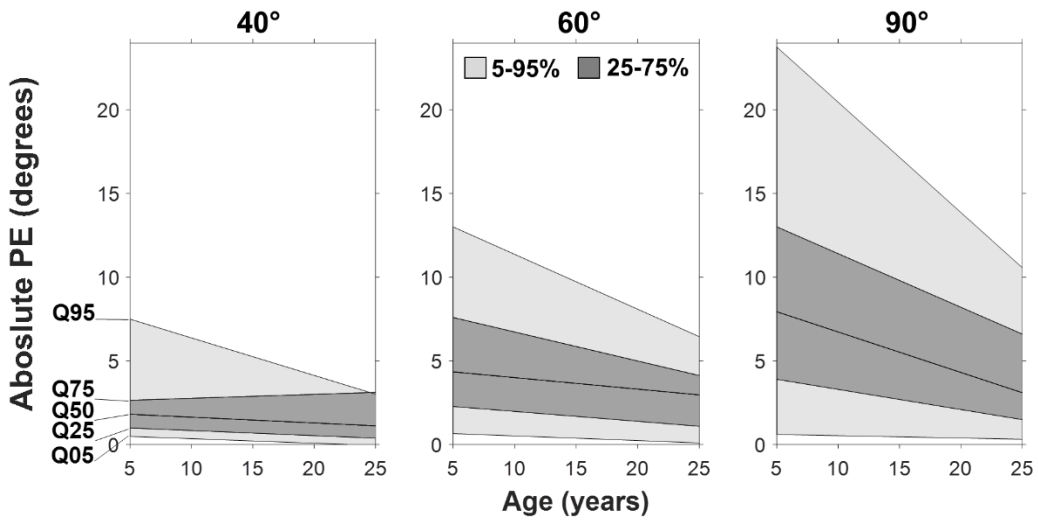

Figure 8: Quantile regression of the absolute value of PE based on the normative cohort. This is the normative data to be used as a comparison with the individuals treated with chemotherapy for pediatric cancer.

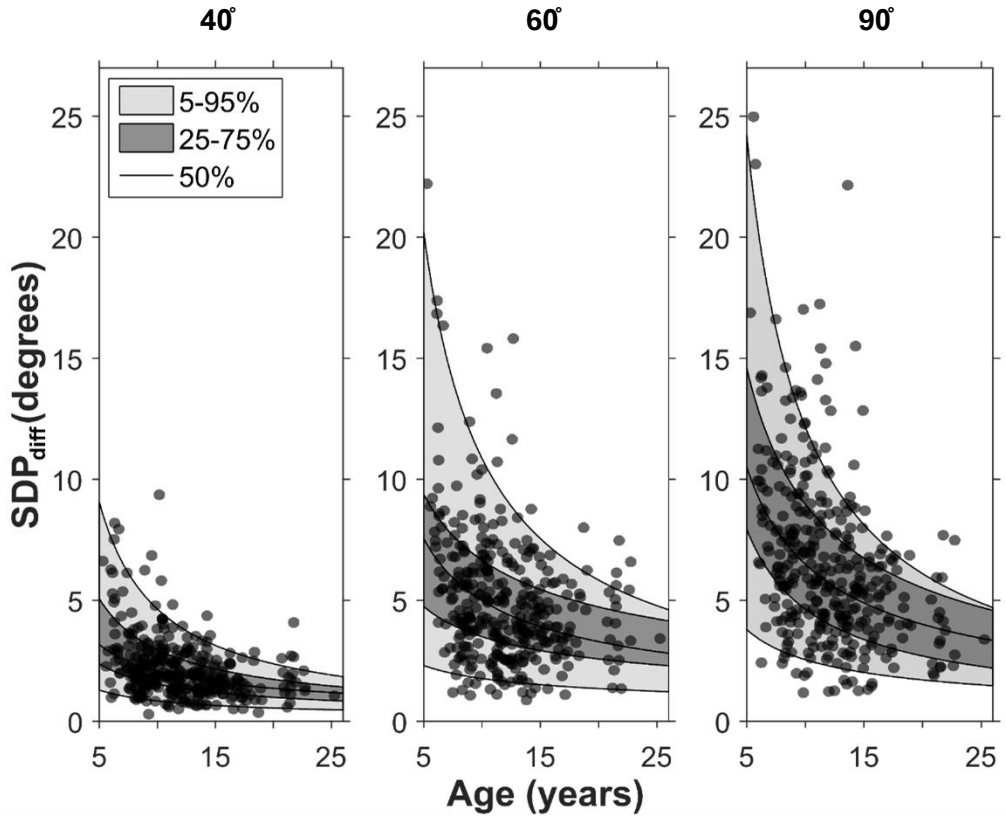

Figure 7: SDP$_{diff}$ from each individual for all three target positions are shown by the circles. The 5th, 25th, 50th, 75th, and 95th percentiles were determined by quantile regression of the SDP$_{diff}$ data by age and are depicted by the lines and shaded areas. Note that precision is age and target position dependent. Modified from Holst-Wolf et al. 2016 Figure 3.

To examine if the age-related trend in SDP_{diff} is associated with any age-related trend in PE, a linear regression for SDP_{diff} with PE as the predictor for each of the three target positions was conducted. All three regressions were significant ($p < 0.05$). However, at most only 12% of the age-related change in SDP_{diff} was explained by PE ($R^2_{adjusted}$: 0.12 for 40º, 0.10 for 60º, and 0.05 for 90º)

Characterizing CIPN-related proprioceptive impairment

To assess impairment in proprioceptive acuity in the patient group, additional linear regression analysis on the control data on the absolute value of the systematic error (PE) by age was performed to generate the percentiles for systematic limb position matching error during development for each of the three target positions. Five individuals (38%) treated with chemotherapy are above the 75th percentile for their age group in at least one target position and one person was above the 95th percentile for the 40º target position (see Figure 7 for normative data, Figure 9 for data from individuals treated with chemotherapy).

Similarly, when comparing limb position precision, 46% of individuals (7 of 15) are above the 75th percentile compared to the age-matched controls for at least one target position and 6 individuals (38%) are above the 95th percentile for at least one position (see Figure10). Five of the adults were above the 75th percentile for two of the target positions. There were no children consistently above the 75th percentile.

To further summarize proprioceptive acuity in this patient group, the average bias, precision, and overall limb position acuity scores (averages of percentiles of the normative cohort for each of the three target positions) were calculated by age group. None of the limb position acuity scores were above the 75th percentile. One bias score and two precision scores were above the 75th percentile, none were above the 95th.

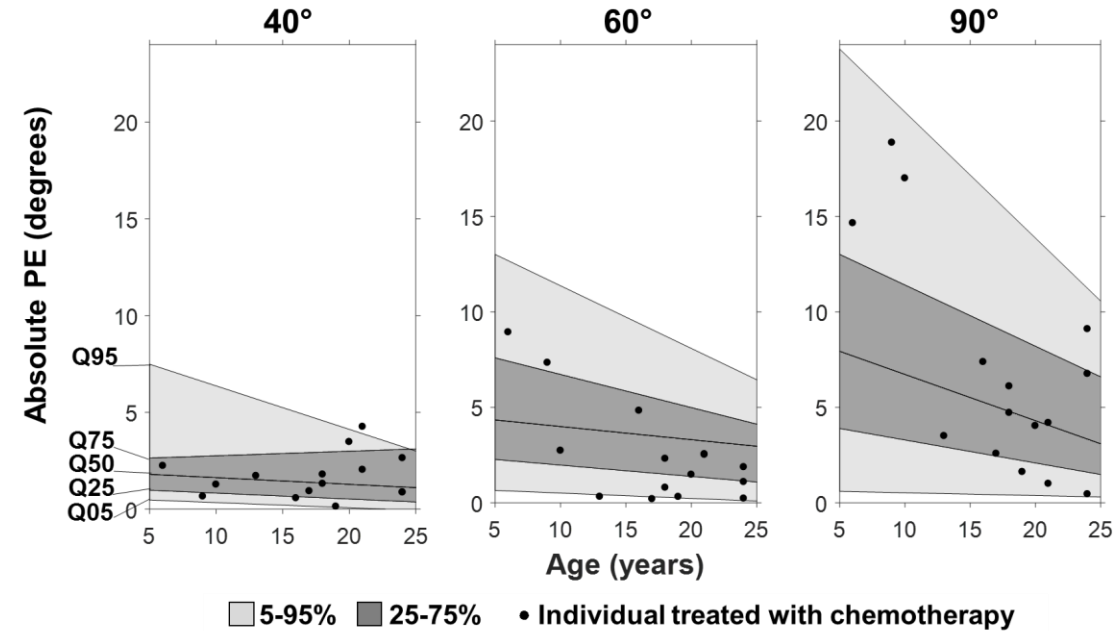

Figure 9: Linear regression analysis for absolute value of PE for the 5th, 25th, 50th, 75th, and 95th percentiles of the normative cohort for the three target positions (40º, 60 º, 90 º). Note there are 6 individuals treated with chemotherapy (circles) with at least one abs(PE) measure above the 75th percentile for their age-matched normative cohort.

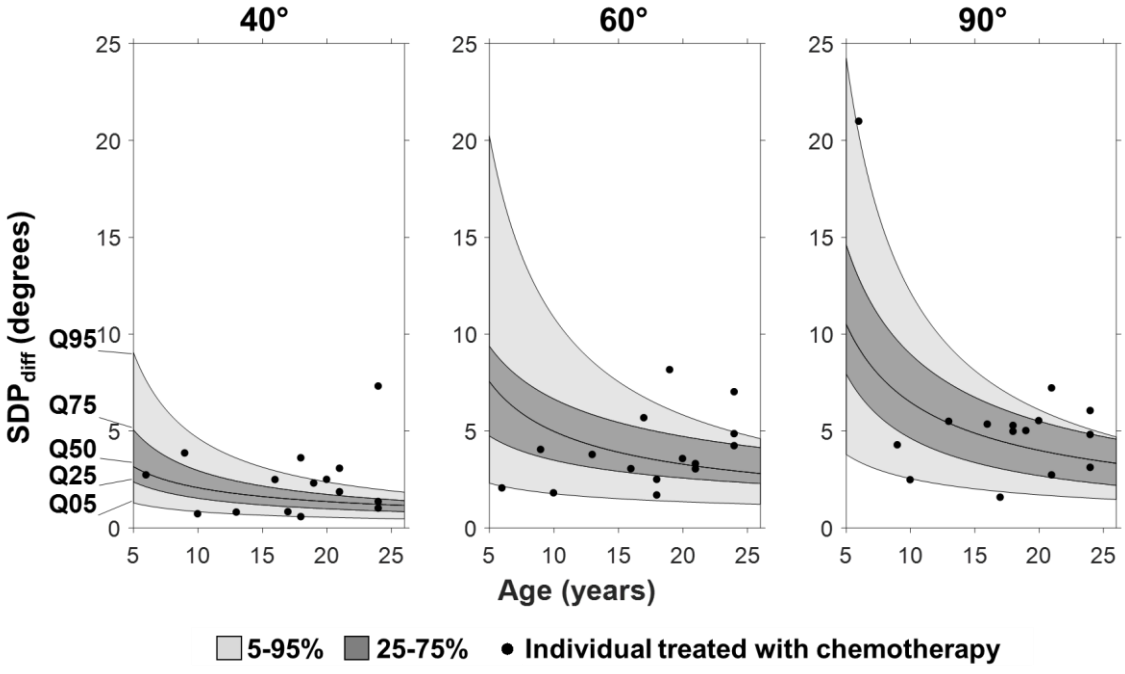

Figure 10: The 5th, 25th, 50th, 75th, and 95th percentiles for the normative cohort of limb position matching precision (SDP_{diff}) by target position (40º, 60 º, 90 º) across age are depicted by the lines and shaded areas. Precision (SDP_{diff}) of each individual treated with chemotherapy for pediatric cancers are the circles. Note 7 individuals treated with chemotherapy have at least one measure above the 95th percentile of the normative cohort.

Haptic acuity and sensitivity in TD children and healthy adults

Haptic acuity and sensitivity data from TD children ages 9 to 12 and adults ages 18 to 25 were collected. It was found that in the age range of 9-12 years, haptic acuity thresholds (discrimination) were not significantly different from those of adults while the haptic sensitivity thresholds (detection) in adults was lower on average, the difference did not reach statistical significance ($p > 0.05$) (Tseng et al. manuscript in preparation 2018). For the individuals in the normative cohort that completed both the discrimination and detection assessments (n = 74), there was no apparent correlation between the two thresholds (linear fit adjusted $R^2 = 0.01$).

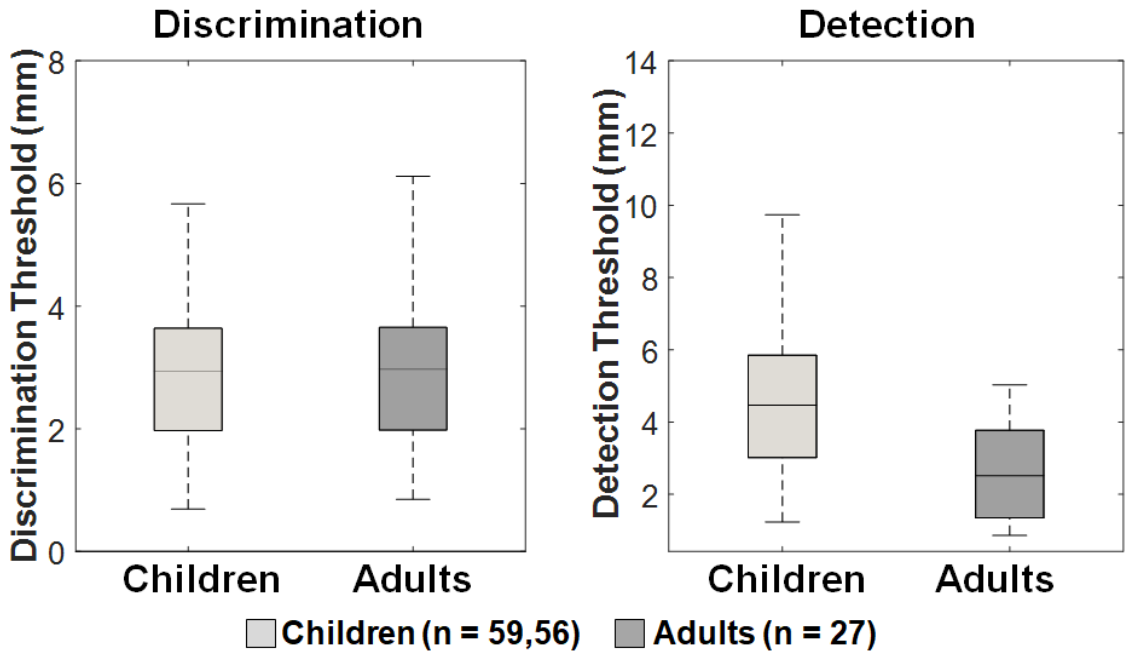

*Figure 11: Boxplots of the haptic discrimination (acuity) and haptic detection (sensitivity) thresholds are shown for the typically developing children (ages 9-12 years) and adult controls. For each boxplot, the center line is the median, the box ranges from the 25th to the 75th percentile and whiskers represent +/- 2.7*SD giving 99.3%. Data were collected in collaboration with Tseng et al.2018. Note there is no apparent developmental trend in this age range.*

Characterizing CIPN-related haptic impairment

To assess haptic impairment in individuals treated with chemotherapy for pediatric cancers the JND thresholds for haptic discrimination (acuity) and detection (sensitivity) m compared with the thresholds of typically developing children and adults in the control group. Most of the individuals treated with chemotherapy, 64% of individuals (9 of 14), had

haptic discrimination (acuity) thresholds above the 75th percentile of the normative data. With respect to haptic detection (sensitivity), 50% of individuals (7 of 14) treated with chemotherapy were above the 75th percentile for their group. Two individuals were distinctly above the 95% for their age matched cohort. In the 14 patients that completed both assessments there was a mild correlation between the discrimination and detection thresholds (linear fit adjusted $R^2 = 0.19$). When looking at the values of both thresholds 11 of the 15 individuals treated with chemotherapy had at least one of the two threshold above the 75th percentile for their age matched cohort and 8 individuals were above the 75th percentile for both thresholds.

An assessment of the scatterplots to identify relationships between the proprioceptive and haptic assessment values found no strong trends (limb position bias score, limb position precision score, limb position acuity score, haptic discrimination JND threshold, and haptic detection JND threshold). The discrimination and detection JND thresholds had the strongest relationship with an adjusted R^2 value of 0.18.

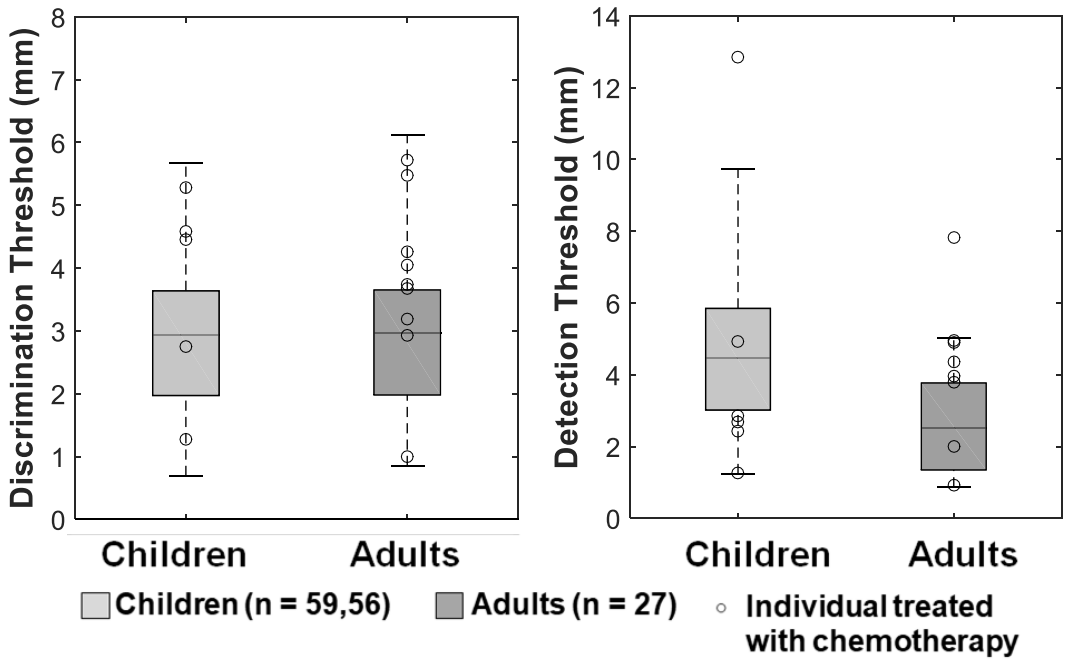

Figure 12: Boxplots of the normative haptic discrimination and detection data for children (ages 9 to 12 years) and adults (ages 19 to 25 years). The circles indicate discrimination or detection thresholds of individuals treated with chemotherapy for pediatric cancers. Individuals in this group ages 6 to 17 are plotted with the children group and individuals ages 18 and older are plotted with the adult data.

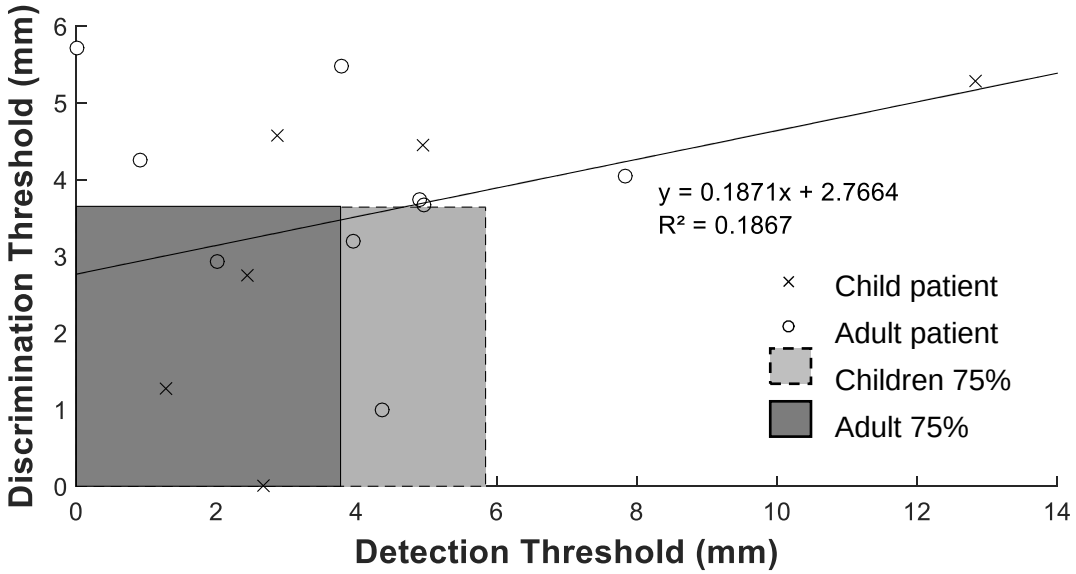

Figure 13: Discrimination and detection thresholds for each individual treated with chemotherapy. The markers on the axes of the graph are the thresholds for the two patients that completed a single haptic assessment. The dark grey box represents the 75th percentiles for the adult normative cohort, the light grey box represents the 75th percentiles for the normative cohort for the children. The solid line is the linear regression fit, the equation and R^2 value for the linear fit are on the graph.

Correlations between CIPN-related somatosensory impairment and demographic, clinical, and therapeutic markers

After verifying the assumptions of each type of statistical analysis, correlation analyses were conducted between the 1) limb position bias score, 2) limb position precision score, 3) the overall limb position acuity score, 4) the haptic discrimination (acuity) JND threshold, and 5) the haptic detection (sensitivity) JND threshold and the clinical treatment variables. For the quantitative clinical treatment variables of age and time since diagnosis (months), none of the Pearson correlation coefficients with the sensory measures listed above were > 0.40. This indicates there were no relationships between the sensory measures and age or time since cancer diagnosis in this sample. To assess a relationship with the categorical treatment variable diagnosis, plots of the mean and 95% confidence interval for each of the five sensory outcomes by diagnosis were created. There were no trends of note between diagnosis and the limb position bias, precision, or overall acuity scores. Haptic discrimination thresholds of individuals diagnosed with leukemia were lower than the other diagnosis groups. Each of the single individuals diagnosed with either malignant neoplasm or Langerhan's cell histiocytosis had higher discrimination thresholds than the other

diagnosis groups. The individual diagnosed with Langerhan's cell histiocytosis had a higher haptic detection threshold than the other groups.

Rather than generate individual correlations between each chemotherapeutic agent type and the sensory measures (as there are 12 agent types applied in unique combinations for each individual) multiple linear regression (MLR) after stepwise variable selection (using Akaike Information Criterion or AIC) was performed to clarify relationships between the sensory measures and the overall cumulative dosage of agents. The agents that were only applied in single individuals were removed (Erwinia, Imatinib, Rituximab, Cranial XRT, and Topotecan). One thing to note, the individual given Imatinib had the highest percentile for the limb position precision score and was above the 75^{th} percentile for both the haptic discrimination thresholds (see Figures 15, 16, and 17). The haptic discrimination and detection thresholds for the individual given Erwinia were both above the 75^{th} percentile for the normative cohort as well (see Figures 16 and 17).

Several agent types appeared in multiple models (antimetabolites, plant alkaloids, alkylating agents, Etoposide, antineoplastics, and glucocorticosteroids). Based on adjusted R^2 value, the models for limb position bias score and precision score are not well explained by cumulative dosage of agent types (see Figures 14 and 15). The best model was the fit of the Haptic Discrimination Thresholds with an adjusted R^2 of 0.80 (see Table 5 for all the MLR model adjusted R^2 values). The signs and magnitudes of the coefficients for plant alkaloids (which includes Vincristine and Vinblastine) and anti-tumor antibiotics in the haptic discrimination threshold MLR model indicates a positive relationship, higher the cumulative dosage of these agents was associated with a higher haptic discrimination threshold (see Table 6 for model coefficients).

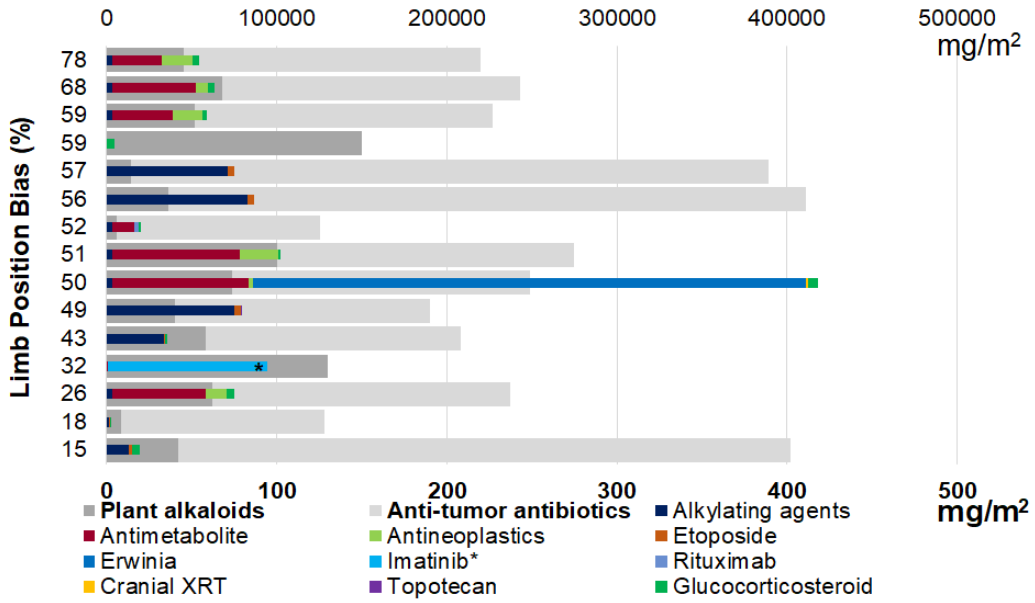

*Figure 14: Cumulative dosage of 12 different types of chemotherapeutic agents arranged by the magnitude of the limb position bias score (%). For this and the following 3 bar graphs, the wide bars are for plant alkaloids and anti-tumor antibiotics associated with the lower (bold) scale and all other agents with the narrow bars are associated with the upper scale. Units of dosage are agent dependent but are typically mg/m². Imatinib is noted with a * because the dosage of this agent is scaled down by a factor of 100 to better fit the scale of rest of the agent dosages in the chart. The agent Topotecan is difficult to see, it was given to the individual with the limb position bias score of 49 (%).*

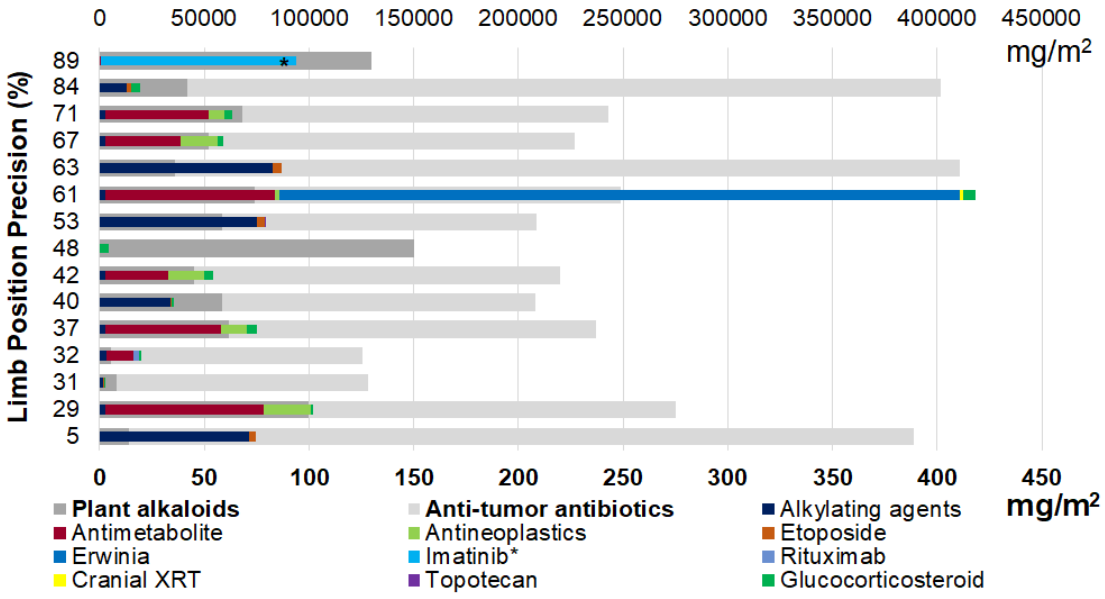

Figure 15: Cumulative dosage of chemotherapeutic agents arranged by the magnitude of the limb position precision score (%). The agent Topotecan is difficult to see, it was given to the individual with the limb position precision score of 53 (%).

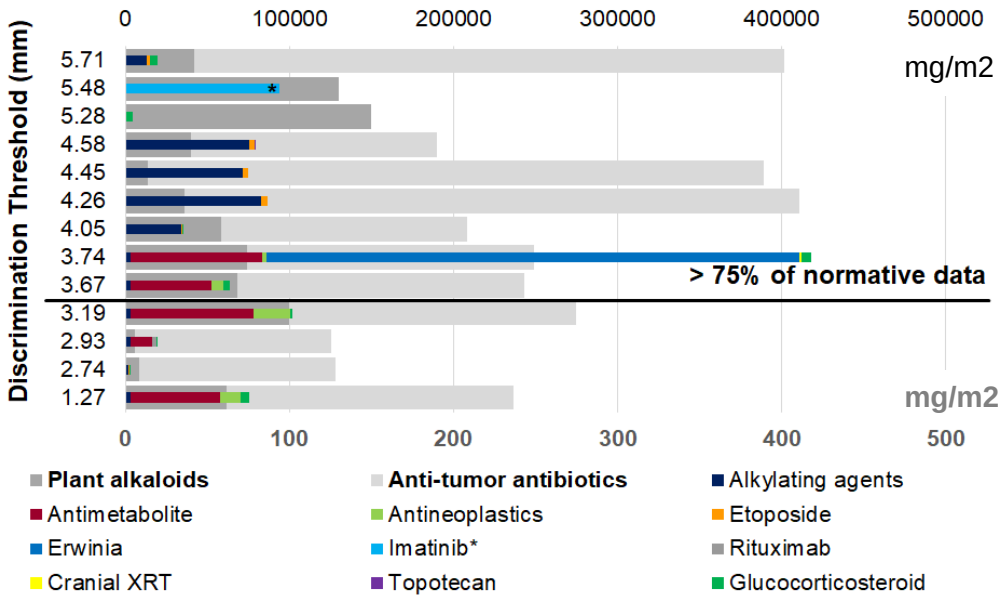

Figure 16: Cumulative dosage of chemotherapeutic agents arranged by the magnitude of the haptic discrimination (acuity) threshold. The agent Topotecan is difficult to see, it was given to the individual with the haptic acuity threshold of 4.58mm. Note that higher doses of plant alkaloids and anti-tumor antibiotics are associated with higher discrimination thresholds.

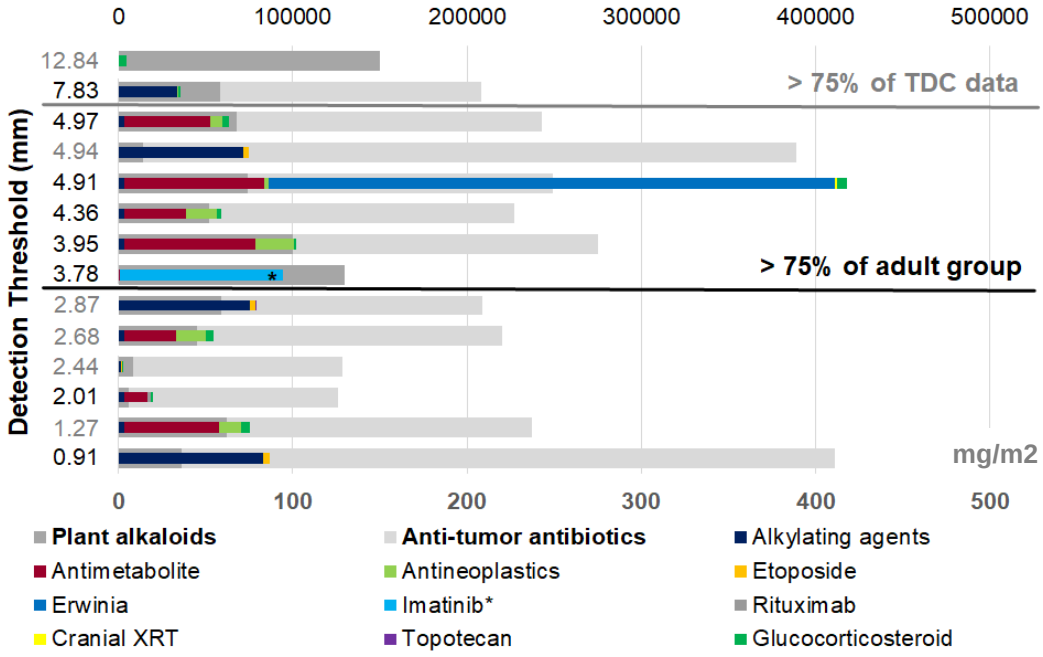

Figure 17: Cumulative dosage of chemotherapeutic agents arranged by the haptic detection (sensitivity) threshold. Thresholds in grey are those of children, thresholds in black are adults. The agent Topotecan is difficult to see, it was given to the individual with the detection threshold of 2.87mm.

Table 5. Summary of the MLR analysis after variable selection of chemotherapeutic agent types for each of the sensory outcomes. The diagnostic residual plots for each model were indicated that a linear fit was appropriate, the residuals were normally distributed, and the assumption of equal variance was met. Significance levels for the agent types are: 0 '***', 0.001 '**', 0.01 '*', 0.05 '^', all else 0.1 ' '.

Sensory Measure	Agent Type	Adjusted R^2
Limb Position Bias Score (Quantile)	Alkylating agents^, Antineoplastics, Etoposide	0.22
Limb Position Precision Score (Quantile)	Alkylating agents, Plant alkaloids, Etoposide	0.12
Limb Position Acuity Score (Quantile)	Plant alkaloids	0.09
Haptic Discrimination JND Threshold	Alkylating agents, Antineoplastics***, Anti-tumor antibiotics**, Plant alkaloids***, Glucocorticosteroid^	0.80
Haptic Detection JND Threshold	Antimetabolite^, Plant alkaloids*, Glucocorticosteroid	0.41

Table 6. MLR model of Haptic Discrimination Threshold coefficient values and statistics.

Coefficients	Estimate	Standard Error	t-value	Pr(>|t|)
(Intercept)	1.624e+00	6.192e-01	2.622	0.030552
Alkylating agents	-1.666e-05	1.081e-05	-1.541	0.161874
Antineoplastics	-1.622e-04	2.749e-05	-5.900	0.000362
Anti-tumor antibiotics	9.625e-03	2.817e-03	3.417	0.009134
Plant alkaloids	3.262e-02	6.086e-03	5.360	0.000678
Glucocorticosteroid	-2.533e-04	1.193e-04	-2.124	0.066451

Discussion

This work applied two somatosensory assessments to characterize the development of proprioceptive and haptic function in typically developing children. In addition, the clinical usefulness of these assessments were examined by applying the tests to small set of individuals treated with chemotherapy for pediatric cancer. The main findings are as follows: First, typical proprioceptive development continues throughout childhood. Second, typical haptic function was not significantly different from adults in the age range assessed here. Third, these assessments identified proprioceptive impairment in 47% and haptic impairment in 73% of the individuals treated with chemotherapy. Fourth, haptic acuity was correlated to cumulative dosage of chemotherapy. These findings are discussed in detail below.

Typical development of proprioception and haptics

Characterizing typical development of proprioception (Aim 1)

To my knowledge, this is the first study that comprehensively and objectively characterizes the development of limb position acuity from early childhood to adulthood using in a cross-sectional design. Limb position matching allowed for the analysis of the two components of limb position acuity, precision and bias. Measurement of these components demonstrated that the development of proprioceptive acuity is characterized by an improvement in precision. Meaning, variability in the sensory responses decreased with age. No trend in bias across development indicated that the systematic error (consistently overshooting or undershooting the target position) did not significantly change in this age range.

The primary mechanoreceptor of limb position sense is the muscle spindle. Muscle spindles are mature in children as early as 3 years of age (Österlund et al. 2011). Spinal level circuitry maturation can be inferred from Hoffman reflex (H-reflex) responses, which are adult-like by 6 to 7 years of age in children (O'Sullivan, Eyre and Miller 1991, Grosset et al. 2007). Similarly, in typically developing children, somatosensory evoked potential (SEP) morphology is mature by the age of 3 years while the latency is not adult-like until ages 6 to 8 years (Laget et al. 1976, Boor, Goebel and Taylor 1998, Boor and Goebel 2000). Pihko et al. found that tactile stimulation induced somatosensory evoked fields approach adult-like behavior by the age of 2 years but the morphology and

latency continue to mature past 6 years of age (Pihko et al. 2005, Pihko et al. 2009). The differences in latencies may indicate maturation of the lemniscal and/or thalamo-cortical somatosensory pathways. Our population is as young as 5 years of age so differences in maturation of the peripheral mechanoreceptors does not completely explain the changes we see. The spinal level and thalamo-cortical pathway maturation may only explain improvement in proprioceptive acuity at the youngest portion of our dataset where we see the greatest differences in proprioceptive precision.

Changes in the sensitivity of muscle spindles may in-part account for improvement of proprioceptive precision during development. Grosset et al. identified differences in the stretch reflex responses during development. They found the stretch reflex amplitude, which is regulated by gamma motorneuron activation, is changing throughout childhood and does not yet reach adult levels by age 11 years (Grosset et al. 2007). Given the spinal-level circuitry are mature at this point in development, information from supraspinal locations that descend to gamma motorneurons affecting the sensitivity of muscle spindles may in-part account for developmental changes in proprioceptive acuity.

Several additional cortical changes may influence the development of proprioception. Nerve axon and dendrite growth as well as changes in the neurotransmitter system occur throughout childhood (Nevalainen, Lauronen and Pihko 2014). There are also specific structures involved in the processing of somatosensory information that are maturing throughout childhood. Nerve axon growth and cytoskeletal changes in the corpus callosum into adulthood are documented (Keshavan et al. 2002, Lebel, Caverhill Godkewitsch and Beaulieu 2010). The callosal projections are involved in the inter-hemispheric transfer of perceptual information, which is required by the limb position matching task used here. This task requires conveying the limb position information on the reference limb to the opposite hemisphere to correctly position the matching arm (Goble et al. 2005, Goble 2010). The development of the corpus callosum during childhood may account for the developmental trends found here measured with a limb position matching task. Recently, tendon-vibration induced illusory movement with fMRI measures investigated the development of proprioceptive cortical networks in adolescence (Cignetti et al. 2016, Fontan et al. 2017). In children ages 7 to 11 years of age, differences in in the level as well as the areas of activation between pre-adolescents and adults have been found. Children and adults both demonstrated

activation in the primary somatosensory and the posterior parietal areas but only the children demonstrated activation in the frontopolar cortex (Fontan et al. 2017). Similarly, before adolescence, the proprioceptive network is mostly mature but refinement continues documented as a shift from diffuse to focal connectivity principally in fronto-striatal connections (Cignetti et al. 2016). These finding suggest that the cortical structures involved in processing of proprioprioceptive information are refined throughout adolescence. In summary, the developmental timelines of gamma motorneuron activation and somatosensory processing are adult-like in childhood but continue to develop throughout adolescence. This timeline is in agreement with the trend in the limb position matching acuity data found here. The majority of improvement in limb position precision occurs by 10 years of age with minor improvements continuing throughout adolescence.

Characterizing typical development of haptic acuity and sensitivity (Aim 2)

Children ages 9-12 years had adult-like haptic acuity thresholds. While the range and average of sensitivity thresholds of children were both larger than the adults were, the groups were not statistically different. This is contrary to previous findings which indicate haptic development occurs throughout childhood and adolescence (Gori et al. 2008, Gori et al. 2012). The first explanation for this contradiction is the limited age range of children assessed here. Both Gori et al. studies included younger children and a larger age range (5-10 years and 6-14 years). In these studies, children younger than 10 had the largest differences in haptic function compared with adults. With the current age range of children 9-12 years old, we noted a non-significant trend in the sensitivity thresholds compared with the adults and this trend may become statistically significant in a younger population.

Another potential explanation for the contradiction in findings with previous literature has to do with the primary sensory modalities required in the different haptic perception tasks. The curvature perception haptic task used here involved lateral movements of the forearm and hand with the index finger in contact with the curved surface. This curvature perception task likely relies on pressure at the fingertip, finger position, and hand/forearm position motion which includes sensory information from skin mechanoreceptors as well as muscle spindle and Ruffini endings. One of the haptic tasks used prior was a haptic aperture task where children were asked to make judgements about the height of pairs of

blocks after grasping them with the thumb and index finger (Gori et al. 2008). The pertinent sensory information for this task is hand position, which is informed by muscle spindle and Ruffini ending information. The haptic curvature assessment via robotic manipulandum employed by Gori et al. 2012 involved movement of the entire arm (mainly proprioceptive information from muscle spindles) as the children were grasping a handle throughout the curvature perception task. The acuity and sensitivity of different sensory modalities (touch information and proprioceptive information) required by these haptic tasks appear to mature at different rates. This may explain the lack of developmental differences found in the age range of 9-12 years when measuring with a haptic task which more evenly emphasizes tactile and proprioceptive information.

Evidence on the developmental timeline of tactile senses suggests that tactile senses develop early. Similar to proprioception, maturation of the peripheral mechanoreceptors involved in touch perception appears to occur early in childhood. In murine models, Merkel cell SA1 receptors and the peripheral and central nervous system circuitry have been found to morphologically mature at or near birth (Woodbury and Koerber 2007). Less is known about the development of Pacinian corpuscles and Ruffini endings as they are more difficult to find in mouse and non-human primate skin (Jenkins and Lumpkin 2017). Study of somatosensory function in kittens found that there were changes in receptive field and force thresholds at 50 days of age but noted these were likely due to changes in nerve fiber myelination and the mechanical properties of the dermis rather than maturation of mechanoreceptors (Beitel, Gibson and Welker 1977). This evidence indicating that peripheral aspects of tactile senses are mature very young. Furthermore, the processing of tactile sensory information may mature earlier than proprioceptive processing. Tactile sensitivity, measured with moving two-point discrimination measures are adult-like by the age of 4 years (Hermann Richard et al. 1996).

We have demonstrated in this study that proprioceptive precision is maturing throughout childhood and adolescence. Haptic tasks that emphasize proprioceptive information like the aperture perception and full-arm-movement curvature perception task may demonstrate greater developmental changes throughout childhood and adolescence because of the emphasis on proprioceptive information. The curvature assessment employed here may emphasize tactile information more evenly with proprioception thus explaining why we did not find significant developmental changes in these haptic

measures in late childhood. The definition of haptics as using active touch to perceive characteristics of objects would support the inclusion of a tactile sense in a haptic assessment such as the haptic curvature assessment employed here where the index finger is in contact with the curved surface.

However, as the haptic tasks employed here requires both tactile and proprioceptive perception we do suspect there would be some developmental changes during childhood with the trend shifted younger. Several of the neurophysiological changes that affect proprioceptive development will be applicable to haptic function. Cortical axon and dendrite growth in somatosensory processing areas and maturation of SEP morphology and latency indicating maturation of thalamo-cortical somatosensory pathways indicate one could expect small but measurable changes in haptic acuity or sensitivity with development in the range of 5 to 18 years of age with the greatest changes found in the youngest children (Nevalainen et al. 2014, Laget et al. 1976, Boor and Goebel 2000, Pihko et al. 2005, Pihko et al. 2009). As the development of haptic acuity is reliant on proprioception, one would expect to see the greatest differences in young children below the age of 9 years. The non-significant trend of TD children with higher sensitivity thresholds than the adults indicates this measure may be more sensitive to developmental changes in haptic ability. A facet of the tactile sensory processing for this specific haptic curvature detection task may occur later in development.

Finally, the haptic assessment applied here allowed individuals to explore the curvature up to 4 times. This differed from the Gori et al. curvature perception method which allowed for only 2 curvature explorations, over and back. Exploring the curvature more times may differentially aid children who have lower proprioceptive precision compared with adults.

Objective assessment of proprioceptive and haptic function in individuals treated with chemotherapy for pediatric cancer

This is the first known application of objective measures of proprioceptive and haptic function in individuals treated with chemotherapy for pediatric cancer. This demonstrates for the first time that these assessments can identify proprioceptive and haptic impairment in this population. These measures may also provide appropriate resolution to begin understanding relationships between specific chemotherapeutic agents and somatosensory ability. The multiple regression model with the cumulative dosage of

chemotherapeutic agents explaining 80% in the variability of the measured haptic discrimination JND thresholds is a promising early result.

Identifying CIPN-related somatosensory impairment (Aim 3)

Each of the proprioceptive and haptic measures identified signs of somatosensory dysfunction in a subset of individuals treated with chemotherapy for pediatric cancers. With regard to proprioceptive acuity, the measures of bias in the patient group were not outside the normative cohort as only one individual was above the 95th percentile for the 40º target position and less than half of the measures were above the 75th percentile. With precision, 46% of individuals were above the 75th percentile and 6 more were above the 95th percentile for at least one measure (one target position). This would suggest that CIPN-related proprioceptive impairment primarily affects limb position precision and does not generate a consistent bias. This is similar to findings in other pediatric patient groups. Children with developmental coordination disorder demonstrate more variability in a forearm limb position matching task as well, although the reasons for the altered proprioceptive precision are different between these two populations (Tseng et al. 2017). Since there was no trend in bias for the individuals treated with chemotherapy the bias score and the overall limb position scores were not informative in this population. The precision score may be the best measure to apply in future work to assess proprioceptive deficits in pediatric patient populations as there were two individuals with precision scores above the 75th percentile. Alternatively, since there is a noted effect of target position, one could simply select one or a subset of the three target limb positions included here to assess proprioceptive precision.

With regard to the haptic assessments, 64% and 50% of individuals had acuity or sensitivity thresholds above the 75th percentile of the normative cohort. Two individuals were above the 95th percentile on the sensitivity assessment. While most of these values are within the normal range, they are in the fourth quartile suggesting a mild sensory impairment. The consistency of the measured haptic thresholds in this small population of individuals treated with chemotherapy and the noted relationships of the haptic acuity thresholds with clinical variables (discussed in the following section) suggest that the haptic assessment may be better suited to measure CIPN.

Relationships between CIPN and clinical variables (Aim 4)

There were no significant relationships between the proprioceptive and haptic assessment measures. The haptic assessment measure of acuity and sensitivity were correlated, the haptic sensitivity threshold predicted 18% of the variability in the acuity threshold. This lack of agreement between measures is somewhat expected, as the population in this study was heterogeneous with regard to age, diagnosis, and treatment factors. This is congruent with current literature on CIPN which notes that individual factors such as age and genetics as well as treatment factors like chemotherapeutic agent type, agent interactions, cumulative dosage, and duration of treatment likely affect the magnitude and type of neuropathy (Moore and Groninger 2013, Han and Smith 2013, Fitzgerald 2017).

Analysis found no statistically significant relationships between the somatosensory measures and individual age in this sample. However, all of the individuals with a proprioceptive precision measure above the 95th percentile and the majority of individuals with haptic acuity and sensitivity thresholds above the 75th percentile were above 18 years of age. This is in agreement with prior assessments of CIPN which have indicated that age appears to correlate with the severity of neuropathy (Moore and Groninger 2013, Fitzgerald 2017). Interestingly, a number of children had very low sensitivity thresholds, 1st quartile. These findings suggests there may be a correlation with somatosensory deficits and age at exposure to chemotherapy. Using a data primarily from murine models, Fitzgerald et al. have proposed a mechanism for age-related neuropathic pain. They have collected evidence that in young rats the, “neuroimmune response is skewed in an anti-inflammatory direction, suppressing the excitation of dorsal horn neurons and preventing the onset of neuropathic pain.” This immune response switches and becomes inflammatory with increasing age (Fitzgerald and McKelvey 2016). While this finding is specific to small fiber neuropathy (pain), there may be a similar effect on the large fiber somatosensory nerves affecting somatosensation. However, this is a proposed mechanism with little data on the presence of this immune response and timeline for this response in humans and no evidence of this immune response effects on large fiber neuropathy.

Similarly, there were no significant statistical relationships in sample between the somatosensory measures and the clinical variables of diagnosis and time since diagnosis.

Haptic discrimination thresholds were correlated with cumulative dosage of several chemotherapeutic agent types. Specifically, higher cumulative dosage of plant alkaloids, which include Vincristine, Vinblastine, and Vinorelbine, was associated with a higher discrimination JND threshold. These agents are known to induce CIPN, often referred to as Vincristine-induced peripheral neuropathy (VIPN) (Jain et al. 2014, Lavoie Smith et al. 2013, M. et al. 2015, Gilchrist and Tanner 2016). Plant alkaloids are antimicrotubule agents that prohibit cells from division and replication, which leads to cell death and affect both sensory and motor neurons (Moore and Groninger 2013). The exact mechanisms of Vincristine neuropathy are still under investigation, but they include mitochondrial dysfunction, loss of intra-epidermal nerve fibers, large diameter sensory nerve damage, and nerve axon degeneration without demyelination (Han et al. 2013, S., D. and D. 2000). Loss of intra-epidermal nerve fibers was commonly associated with the use of several types of chemotherapeutic agents as well as being common to other peripheral neuropathies, such as diabetic neuropathy (Han and Smith 2013). This may explain why a haptic assessment, which requires tactile perception and proprioception from distal mechanoreceptors, had the best correlation to cumulative dosage of chemotherapeutic agents.

Limitations and alternative explanations

Our proprioceptive acuity assessment is appropriate for children ages 5 years and older, but it likely is not appropriate for younger children as their attention span and understanding of the limb matching task may be limited. The youngest participants in the normative cohort for the haptic assessments were 9 years of age. Sufficient data on younger children is not currently available, only one individual in the patient group aged 6 years completed the haptic assessments. Given the simplicity of the assessment it is anticipated that young children can successfully complete the assessments. While the haptic assessments require more time to complete, with breaks this should be manageable for children as young as 5 years. Unfortunately, the typical vocabulary and attention span of children younger than 5 years limits their ability to understand the assessment instructions and the ability to attend to perception during the entire test. This is a significant limitation as the need for objective, quantitative, high-resolution sensory assessments in pediatric populations younger than the age of 5 remains. For example,

the majority of pediatric patients treated with chemotherapy for lymphoblastic leukemia are younger than the age of 5 during treatment (Lavoie Smith et al. 2013).

The ability of the model for cumulative dosage of chemotherapeutic agents to predict the effects of individual agents on haptic discrimination JND threshold is limited. The prescription of these agent types is not entirely independent, for example, glucocorticosteroids are often given with antimetabolites and Etoposide with alkylating agents. This means the estimates of the relationship of the discrimination threshold with individual coefficients must be interpreted with caution as this does not fit the model assumptions. However, the entire model is not voided, the variables included as a whole do provide for 80% of the variance in the haptic discrimination JND thresholds.

The individuals in this study that were receiving chemotherapy were also receiving other pharmacological agents in addition to chemotherapy. Their prescriptions were reviewed for concurrent usage of benzodiazepines, which are known to affect proprioception, but there may be other pharmacological agents that have similar effects when used alone or with other agents that are not yet recognized. All of the individuals in the group treated with chemotherapy were volunteers from an outpatient clinic. There could be a sampling bias with regard to the severity of neuropathy measured with the somatosensory measures applied here since all of these individuals felt well enough to volunteer to participate in a research study.

Recommendations

The development of proprioceptive acuity continues throughout adolescence into adulthood. Thus, it is important for somatosensory measures to have appropriate normative data across development for comparison with pediatric patient populations. Further work to develop assessments and normative data for proprioceptive acuity of the wrist and lower extremity (ankle assessment) would likely be an asset for measuring peripheral neuropathy since peripheral neuropathy generally affects the longest fibers and thus the distal portions of the body first (Moore and Groninger 2013, Han and Smith 2013). Additionally, assessments for children younger than five years of age are a logical next step. Early identification of sensory impairment is especially relevant in a pediatric populations as sensory dysfunction is occurring during somatosensory development, which is shown here to be incomplete until late adolescence (Holst-Wolf, Yeh and Konczak

2016). This is potentially a critical window as tactile and proprioceptive afferents are required for intact motor behavior such as fine motor control and balance. These temporary or long-term sensory deficits may impair or delay the achievement of developmental motor milestones throughout childhood. If neglected, this could result in negative psychological and social consequences making the early detection of individuals that may benefit from sensorimotor intervention an important component of long-term care.

Given the somatosensory measures used here are quick, objective, and easy to perform in a clinic setting, the proposed proprioceptive and haptic assessments have the potential to become useful tools to identify and monitor long-term somatosensory dysfunction. Here, the haptic discrimination assessment appears best suited to further determine the relationships between chemotherapy and somatosensory ability. Further work to verify the efficacy of the haptic assessments and proprioceptive acuity assessment to identify relationships between sensory impairment and chemotherapy is recommended.

These objective assessments of somatosensory dysfunction in patients with pediatric cancer have the potential to aid clinicians in making informed decisions about the administration of chemotherapeutic agents. If correlations between specific chemotherapeutic agents or other treatment variables and sensory dysfunction are found, this additional information may be used to alter treatment decisions in an attempt to reduce negative sensory consequences. It is anticipated that future studies will determine if sensorimotor deficits improve in long-term follow-up of patients or normalize following completion of therapy. Studies investigating the efficacy of sensorimotor interventions in survivors of pediatric cancers to either aid in a return to pre-treatment sensory ability or to help shorten the period of sensory recovery would also be warranted. The objective sensory measures proposed here may also be useful for the identification and monitoring of other patient populations with known or potential sensory dysfunction such as individuals with other forms of pediatric cancers, adult cancers, or other neurological disease or disorder that affect peripheral nerves such as diabetes.

Conclusion

The typical development of proprioceptive acuity measured by a limb position matching task is best described as an improvement in precision, or the reduction of variability in proprioceptive perception. Larger improvements in limb position precision occur before the age of 10 years and behavior continues to approach that of adults throughout adolescence. Haptic acuity and sensitivity as measured by curvature assessment tasks with the index finger do not demonstrate significant developmental changes between the age of 9 years and adulthood. Further work to assess a younger population is recommended to complete the characterization of haptic development in childhood. Both the proprioceptive and haptic assessments successfully identified somatosensory deficits in individuals treated with chemotherapy for pediatric cancers. While there were no apparent trends between the sensory measures and patient age, diagnosis, or time since diagnosis, all individuals in this study have a unique combination of these factors and a larger sample may be better suited to find relationships between these variables. The haptic acuity assessment measure of JND discrimination threshold did successfully identify a relationship between CIPN and cumulative dosage of chemotherapeutic agent types. Work to further establish the efficacy of these assessments is recommended as there is a significant need in pediatric oncology, and neurology in general, for objective sensory measures suitable for use in the clinic with sufficient resolution to characterize the magnitude of neuropathy.

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Appendix I

Table 7: Cumulative dosage of chemotherapeutic agents

Age	Plant alkaloids	Anti-tumor antibiotics	Alkylating agents	Anti-metabolite	Anti-neoplastics	Etoposide	Erwinia	Imatinib	Rituximab	Cranial XRT	Topotecan	Glucocortico-steroid
6	45	175	3000	29671	17500	NA	NA	NA	NA	NA	NA	4020
9	150	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	4650
10	14	375	71400	NA	NA	3500	NA	NA	NA	NA	NA	0
13	62	175	3000	54940	12500	NA	NA	NA	NA	NA	NA	4890
16	40	150	75250	NA	NA	3500	NA	NA	NA	NA	18.75	0
17	8.28	120	1600	NA	NA	625	NA	NA	NA	NA	NA	400
18	100	175	3000	75280	22500	NA	NA	NA	NA	NA	NA	1268
18	36	375	82800	NA	NA	4000	NA	NA	NA	NA	NA	0
19	42	360	12800	NA	NA	2400	NA	NA	NA	NA	NA	4480
20	52	175	3000	35710	17500	NA	NA	NA	NA	NA	NA	2620
21	58.4	150	33900	NA	36	600	NA	NA	NA	NA	NA	840
21	68	175	3000	49300	7500	NA	NA	NA	NA	NA	NA	3820
24	130	NA	NA	780	NA	NA	NA	934200	NA	NA	NA	0
24	5.73	120	3300	13165	NA	NA	NA	NA	2250	NA	NA	1155
25	74	175	3000	80615	2500	NA	325000	NA	NA	1200	NA	6020

Table 8.1 Cumulative dosage of chemotherapeutic agents with individual units.

	Alkylating Agents				Antineoplastics		Anti-tumor Antiobiotics			
Age	**Ifosfamide**	**Procarbazine**	**Cyclophos-phamide**	**Carmustine**	**Brentuximab**	**PEG-asparaginase**	**Anthracycline (doxo equivalents)**	**Bleomycin**	**Erwinia**	**Rituximab**
yrs	mg/m^2	mg/m^2	mg/m^2	mg/m^2	mg/kg	IU/m^2	mg/m^2	U/m2	IU/m^2	mg/m^2
6			3000			17,500	175			
9										
10	63,000		8400				375			
13			3000			12,500	175			
16	63,000		12,250				150			
17			1600				100	20		
18	72,000		10,800				375			
18			3000			22500	175			
19		5600	7200				280	80		
20			3000			17500	175			
21	24,000		9600	300	36		150			
21			3000			7500	175			
24										
24			3300				120			2250
25			3000			2500	175		325000	

Table 8.2 Cumulative dosage of chemotherapeutic agents with individual units continued.

	Antimetabolites									
Age	**Nelarabine**	**IT Methotrexate**	**IV Methotrexate**	**PO Methotrexate**	**Mercapto-purine**	**Thioguanine**	**Cytarabine**	**IT ara-c**	**Imatinib**	**Etoposide**
yrs	mg/m^2	mg	mg/m^2	mg/m^2	mg/m^2	mg/m^2	mg/m^2	mg	mg	mg/m^2
6		216	1000	740	25,005	840	1800	70		
9										
10										3500
13		300	20,000	860	30,530	840	1800	610		
16										3500
17										625
18										4000
18		390	1000	2300	68,880	840	1800	70		
19										2400
20		240	21000	280	11480	840	1800	70		
21										600
21		285	21,000	700	24,605	840	1800	70		
24			780						934,200	
24		105	12,000				1000	60		
25	9750	255	20,000	1560	47180		1800	70		

Table 8.3 Cumulative dosage of chemotherapeutic agents with individual units continued.

		Plant Alkaloids				Glucocorticosteroid		
Age	**Vinblastine**	**Vincristine**	**Vinorelbine**	**Topotecan**	**Cranial XRT**	**Prednisone**	**Dexamethasone**	**IT Hydrocortisone**
yrs	mg/m^2	mg/m^2 or mg	mg/m^2	mg/m^2	cGy	mg/m^2	mg/m^2	mg
6		45				3880	140	
9	150					4650		
10		14						
13		62				4480	140	270
16		40		18.75				
17		8.28				400		
18		36						
18		100					1268	
19	24	18				4480		
20		52				2480	140	
21		8.4	50			840		
21		68				3680	140	
24	130							
24		5.73				1020		135
25		74			1200	5880	140	

Appendix II

Figure 18: The percentiles (by age group) for each of the three summary limb position acuity scores for each individual treated with chemotherapy for pediatric cancer ordered from left to right by chronological age. Note, none of these scores are consistently over the 75th percentile.